

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Braftovi 50 mg hard capsules

Braftovi 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Braftovi 50 mg hard capsules

Each hard capsule contains 50 mg of encorafenib.

Braftovi 75 mg hard capsules

Each hard capsule contains 75 mg of encorafenib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Braftovi 50 mg hard capsules

Orange opaque cap and flesh opaque body, printed with a stylised “A” on the cap and “LGX 50mg” on the body. The length of the capsule is approximately 22 mm.

Braftovi 75 mg hard capsules

Flesh coloured opaque cap and white opaque body, printed with a stylised “A” on the cap and “LGX 75mg” on the body. The length of the capsule is approximately 23 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Colorectal cancer (CRC)

- Encorafenib in combination with cetuximab is indicated 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 cetuximab and FOLFOX is indicated for the first line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation.

Non-small cell lung cancer (NSCLC)

Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation.

For biomarker-based patient selection, see section 4.2

4.2 Posology and method of administration

Encorafenib treatment should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.

Patient selection

Before taking encorafenib, patients must have confirmation of BRAF V600E mutation assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used.

The efficacy and safety of encorafenib have been established only in patients with melanoma tumours expressing BRAF V600E and V600K mutations, colorectal tumours expressing a BRAF V600E mutation or NSCLC expressing a BRAF V600E mutation. Encorafenib should not be used in patients with wild type BRAF malignant melanoma, wild type BRAF colorectal cancer or wild-type BRAF NSCLC.

Posology

Melanoma and NSCLC

The recommended dose of encorafenib is 450 mg (six 75 mg capsules) once daily, when used in combination with binimetinib.

Colorectal cancer

The recommended dose of encorafenib is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab (weekly administration), or in combination with cetuximab (bi-weekly administration) and FOLFOX. For the dosage or recommended dose modifications of concomitantly administered chemotherapeutic agents and cetuximab, refer to the product information for these medicinal products.

Dose modification

Melanoma and NSCLC

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 1, 3 and 4).

For information on the posology and recommended dose modifications of binimetinib, see section 4.2 of binimetinib Summary of Product Characteristics (SmPC).

Dose reduction recommendations for encorafenib are presented in Table 1.

Table 1: Recommended dose modifications for encorafenib when used in combination with binimetinib in melanoma or NSCLC indications

Dose level	Encorafenib dose when used in combination with binimetinib
Starting dose	Six 75 mg (450 mg) capsules once daily
1 st dose reduction	Four 75 mg (300 mg) capsules once daily
2 nd dose reduction	Three 75 mg (225 mg) capsules once daily
Subsequent modification	For melanoma indication: There are limited data for dose reduction to 100 mg once daily. Encorafenib should be permanently discontinued if patient is unable to tolerate 100 mg (two 50 mg capsules) once daily. For NSCLC indication: Encorafenib should be permanently discontinued if patient is unable to tolerate 225 mg (three 75 mg capsules) once daily.

Administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced to 300 mg once daily during the time of binimetinib dose interruption (see section 4.2 of binimetinib SmPC) as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued.

If encorafenib is temporarily interrupted (see Tables 3 and 4), binimetinib should be interrupted. If encorafenib is permanently discontinued, then binimetinib should be discontinued.

If treatment-related toxicities occur, then encorafenib and binimetinib should be dose reduced, interrupted or discontinued. Dose modifications are necessary for binimetinib only (adverse reactions primarily related to binimetinib) for the following: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), interstitial lung disease/pneumonitis, cardiac dysfunction, creatine phosphokinase (CK) elevation and rhabdomyolysis, and venous thromboembolism (VTE). If one of these toxicities occurs, see section 4.2 of binimetinib SmPC for dose modification instructions for binimetinib.

Colorectal cancer

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation of encorafenib (see Tables 2, 3 and 4).

For information on the posology and recommended dose modifications of cetuximab and FOLFOX (5-fluorouracil/folinic acid/oxaliplatin), please refer to respective medicines SmPC.

Dose reduction recommendations for encorafenib are presented in Table 2.

Table 2: Recommended dose modifications for encorafenib when used in combination with cetuximab or in combination with cetuximab and FOLFOX in CRC indication

Dose level	Encorafenib dose when used in combination with cetuximab or in combination with cetuximab and FOLFOX
Starting dose	Four 75 mg (300 mg) capsules once daily
1 st dose reduction	Three 75 mg (225 mg) capsules once daily
2 nd dose reduction	Two 75 mg (150 mg) capsules once daily Encorafenib should be permanently discontinued if patient is unable to tolerate 150 mg (two 75 mg capsules) once daily.

If encorafenib is permanently discontinued, cetuximab should be discontinued. FOLFOX alone may be continued per standard of care.

If cetuximab is permanently discontinued, encorafenib should be discontinued. FOLFOX alone may be continued per standard of care.

If FOLFOX is permanently discontinued, the combination of encorafenib and cetuximab may be continued.

Melanoma, colorectal cancer and NSCLC

Dose modifications in case of adverse reactions are provided below and in Tables 3 and 4.

For new primary cutaneous malignancies: No dose modifications are required for encorafenib.

For new primary non-cutaneous RAS mutation-positive malignancies: it should be considered to discontinue encorafenib permanently.

Table 3: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab or in combination with cetuximab and FOLFOX for selected adverse reactions

Severity of adverse reaction ^a	Encorafenib
<i>Cutaneous reactions</i>	
Grade 2	Encorafenib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib should be withheld until Grade 0 or 1 and then resumed at the same dose.
Grade 3	Encorafenib should be withheld until improved to Grade 0 or 1 and resumed at the same dose if first occurrence, or resumed at a reduced dose if recurrent Grade 3.
Grade 4	Encorafenib should be permanently discontinued.
<i>Palmar-plantar erythrodysesthesia syndrome (PPES)</i>	
Grade 2	Encorafenib should be maintained and supportive measures such as topical therapy should be instituted. If not improved despite supportive therapy within 2 weeks, encorafenib should be withheld until improved to Grade 0 or 1 and treatment should be resumed at same dose level or at a reduced dose.
Grade 3	Encorafenib should be withheld, supportive measures such as topical therapy should be instituted, and the patient should be reassessed weekly. Encorafenib should be resumed at same dose level or at a reduced dose level when improved to Grade 0 or 1.
<i>Uveitis including iritis and iridocyclitis</i>	
Grade 1-3	If Grade 1 or 2 uveitis does not respond to specific (e.g. topical) ocular therapy or for Grade 3 uveitis, encorafenib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. If uveitis is Grade 1 and it improves to Grade 0, then treatment should be resumed at the same dose. If uveitis is Grade 2 or 3 and it improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, ophthalmic monitoring should be repeated and encorafenib should be permanently discontinued.
Grade 4	Encorafenib should be permanently discontinued and a follow up with ophthalmologic monitoring should be performed.

Severity of adverse reaction ^a	Encorafenib
<i>QTc Prolongation</i>	
• QTcF > 500 ms and change ≤ 60 ms from pre-treatment value	Encorafenib should be withheld (see monitoring in section 4.4). Encorafenib should be resumed at a reduced dose when QTcF ≤ 500 ms. Encorafenib should be discontinued if more than one recurrence.
• QTcF > 500 ms and increased by > 60 ms from pre-treatment values	Encorafenib should be permanently discontinued (see monitoring in section 4.4).
<i>Liver laboratory abnormalities</i>	
• Grade 2 (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x ≤ 5x upper limit of normal (ULN))	Encorafenib should be maintained. If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resumed at the same dose.
• First occurrence of Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 (AST or ALT > 5x ULN and blood bilirubin > 2x ULN)	It should be considered to permanently discontinue encorafenib.
• Recurrent Grade 4 (AST or ALT > 20 ULN)	Encorafenib should be permanently discontinued.

^a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Table 4: Recommended dose modifications for encorafenib when used in combination with binimetinib or in combination with cetuximab or in combination with cetuximab and FOLFOX for other adverse reactions

Severity of adverse reaction	Encorafenib
• Recurrent or intolerable Grade 2 adverse reactions • First occurrence of Grade 3 adverse reactions	Encorafenib should be withheld for up to 4 weeks. • If improved to Grade 0 or 1 or to baseline levels, it should be resumed at a reduced dose. • If not improved, encorafenib should be permanently discontinued
• First occurrence of any Grade 4 adverse reaction	Encorafenib should be withheld for up to 4 weeks • If improved to Grade 0 or 1 or to baseline levels, then it should be resumed at a reduced dose level. • If not improved, encorafenib should be permanently discontinued. Or, encorafenib should be permanently discontinued.
• Recurrent Grade 3 adverse reactions	Permanent discontinuation of encorafenib should be considered.
• Recurrent Grade 4 adverse reactions	Encorafenib should be permanently discontinued.

Duration of treatment

Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.

Missed doses

If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.

Vomiting

In case of vomiting after administration of encorafenib, the patient should not take an additional dose and should take the next scheduled dose.

Special populations

Elderly patients

No dose adjustment is required for patients aged 65 years and older (see section 5.2).

Hepatic impairment

Patients with mild to severe hepatic impairment may have increased encorafenib exposure (see section 5.2).

Administration of encorafenib should be undertaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment (Child-Pugh Class A).

No dosing recommendation can be made in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment based on a population pharmacokinetics (PK) analysis. There are no clinical data with encorafenib in patients with severe renal impairment. Therefore, the potential need for dose adjustment cannot be determined. Encorafenib should be used with caution in patients with severe renal impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of encorafenib have not yet been established in children and adolescents. No data are available.

Method of administration

Braftovi is for oral use. The capsules are to be swallowed whole with water. They may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided (see sections 4.4 and 4.5).

For patients unable to swallow, Braftovi capsules may be opened and the content dispersed in a small quantity (approximately 20 mL) of apple sauce and taken immediately.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Encorafenib is to be given in combination with binimetinib (for patients with BRAF V600 mutant unresectable or metastatic melanoma, and for patients with BRAF V600E mutant advanced NSCLC), or in combination with cetuximab (for patients with BRAF V600E mutant metastatic colorectal cancer who have received prior systemic therapy), or in combination with cetuximab and FOLFOX (for first line treatment of patients with BRAF V600E mutant metastatic colorectal cancer). For additional information on warnings and precautions associated with binimetinib, cetuximab, 5-fluorouracil, folinic acid or oxaliplatin treatment, see section 4.4 of respective medicines SmPC.

Encorafenib in combination with binimetinib in patients who have progressed on a BRAF inhibitor

There are limited data for the use of the combination of encorafenib with binimetinib in patients who have progressed on a prior BRAF inhibitor given for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. These data show that the efficacy of the combination would be lower in these patients.

Encorafenib in combination with binimetinib in patients with brain metastases

There are limited efficacy data with the combination of encorafenib and binimetinib in patients with a BRAF V600 mutant melanoma or BRAF V600E mutant NSCLC which have metastasised to the brain (see section 5.1).

Left ventricular dysfunction (LVD)

LVD defined as symptomatic or asymptomatic decreases in ejection fraction has been reported when encorafenib is used in combination with binimetinib. It is recommended that left ventricular ejection fraction (LVEF) is assessed by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of encorafenib and binimetinib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. If during treatment LVD occurs, see section 4.2 of binimetinib SmPC.

The safety of encorafenib in combination with binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. Therefore, in these patients, binimetinib should be used with caution and for any symptomatic left ventricular dysfunction, Grade 3-4 LVEF decrease or for absolute decrease of LVEF from baseline of $\geq 10\%$, binimetinib and encorafenib should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

Haemorrhage

Haemorrhages, including major haemorrhagic events, can occur with encorafenib (see section 4.8). The risk of haemorrhage may be increased with concomitant use of anticoagulant and antiplatelet therapy. The occurrence of Grade ≥ 3 haemorrhagic events should be managed with dose interruption or treatment discontinuation (see Table 4 in section 4.2) and as clinically indicated.

Ocular toxicities

Ocular toxicities including uveitis, iritis, and iridocyclitis can occur when encorafenib is administered. RPED has also been reported in patients treated with encorafenib in combination with binimetinib (see section 4.8).

Patients should be assessed at each visit for symptoms of new or worsening visual disturbance. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended.

If uveitis including iridocyclitis and iritis occurs during treatment, see section 4.2.

If during treatment patient develops RPED or RVO, see section 4.2 of binimetinib SmPC for guidance.

QT prolongation

QT Prolongation has been observed in patients treated with BRAF-inhibitors. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted.

Overall, results suggest that single agent encorafenib has the potential to cause mild increases in heart rate. Across pooled combination studies of encorafenib and binimetinib at the recommended doses and a single-agent encorafenib study, results suggest that encorafenib has the potential to result in small increases in QTc interval (see section 5.1).

There are insufficient data to exclude a clinically significant exposure dependent QT prolongation. Due to the potential risk for QT prolongation, it is recommended that serum electrolytes abnormalities, including magnesium and potassium, are corrected and risk factors for QT prolongation controlled (e.g. congestive heart failure, bradyarrhythmias) before treatment initiation and during treatment. It is recommended that an electrocardiogram (ECG) is assessed before initiation of encorafenib, one month after initiation, and then at approximately 3-month intervals or more frequently as clinically indicated, while on treatment. The occurrence of QTc prolongation can be managed with dose reduction, interruption or discontinuation with correction of abnormal electrolytes and control of risk factors (see section 4.2).

New primary malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur when encorafenib is administered (see section 4.8).

Cutaneous malignancies

Cutaneous malignancies such as cutaneous squamous cell carcinoma (cuSCC) including keratoacanthoma have been observed in patients treated with BRAF-inhibitors including encorafenib. New primary melanoma has been observed in patients treated with BRAF inhibitors including encorafenib (see section 4.8).

Dermatologic evaluations should be performed prior to initiation of therapy with encorafenib, every 2 months while on therapy and for up to 6 months following treatment discontinuation. Suspicious skin lesions should be managed with dermatological excision and dermatopathologic evaluation. Patients should be instructed to immediately inform their physicians if new skin lesions develop. Encorafenib should be continued without any dose modification.

Non-cutaneous malignancies

Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Patients receiving encorafenib should undergo a head and neck examination, chest/abdomen computerised tomography (CT) scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of

treatment as clinically appropriate. It should be considered to permanently discontinue encorafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. Benefits and risks should be carefully considered before administering encorafenib to patients with a prior or concurrent cancer associated with RAS mutation.

Tumour lysis syndrome (TLS)

The occurrence of TLS, which may be fatal, has been associated with the use of encorafenib in association with binimetinib (see section 4.8). Risk factors for TLS include high tumour burden, preexisting chronic renal insufficiency, oliguria, dehydration, hypotension and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.

Liver laboratory abnormalities

Liver laboratory abnormalities including AST and ALT elevations have been observed with encorafenib (see section 4.8). Liver laboratory values should be monitored before initiation of encorafenib and monitored at least monthly during the 6 first months of treatment, then as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see section 4.2).

Hepatic impairment

As encorafenib is primarily metabolised and eliminated via the liver, patients with mild to severe hepatic impairment may have increased encorafenib exposure over the range of inter-subject variability exposure (see section 5.2).

In the absence of clinical data, encorafenib is not recommended in patients with moderate or severe hepatic impairment.

Administration of encorafenib should be undertaken with caution at a dose of 300 mg once daily in patients with mild hepatic impairment (see section 4.2).

Closer monitoring of encorafenib related toxicities in patients with mild hepatic impairment is recommended, including clinical examination and liver function tests, with assessment of ECGs as clinically appropriate during treatment.

Renal impairment

There are no data available in patients with severe renal impairment (see sections 4.2 and 5.2).

Encorafenib should be used with caution in patients with severe renal impairment. Creatinine elevation has been commonly reported with encorafenib as single agent or in combination with binimetinib or cetuximab. Observed cases of renal failure including acute kidney injury and renal impairment were generally associated with vomiting and dehydration. Other contributing factors included diabetes and hypertension. Blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation (see Table 4 in section 4.2). Patients should ensure adequate fluid intake during treatment.

Effects of other medicinal products on encorafenib.

Concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety (see section 4.5).

Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on encorafenib

Encorafenib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors

Co-administration of moderate (diltiazem) and strong (posaconazole) CYP3A4 inhibitors with single doses of encorafenib in healthy volunteers resulted in a 2 and 3-fold increase in the area under the concentration-time curve (AUC), respectively and in 44.6% and 68.3% increase in maximum encorafenib concentration ($C_{\max}$) respectively.

Model based predictions indicate that the effect of posaconazole after repeated administrations could be similar for AUC (3-fold increase) and slightly greater for $C_{\max}$ (2.7-fold increase). Model-based predictions for ketoconazole suggest an increase of approx. 5-fold for encorafenib AUC and 3 to 4-fold for encorafenib $C_{\max}$ after administration of encorafenib 450 and 300 mg QD, respectively.

Therefore, concomitant administration of encorafenib with strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity, see section 5.2).

Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. If concomitant use of a strong CYP3A inhibitor is unavoidable, patients should be carefully monitored for safety.

Moderate CYP3A4 inhibitors should be co-administered with caution. Examples of moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, diltiazem, amprenavir and imatinib. When encorafenib is co-administered with a moderate CYP3A inhibitor, patients should be carefully monitored for safety.

CYP3A4 inducers

Co-administration of encorafenib with a strong CYP3A4 inducer was not assessed in a clinical study; however, a reduction in encorafenib exposure is likely and may result in compromised efficacy of encorafenib. Examples of strong CYP3A4 inducers include, but are not limited to carbamazepine, rifampicin, phenytoin and St. John's Wort. Alternative agents with no to moderate CYP3A induction potential should be considered.

Effects of encorafenib on other medicinal products

CYP substrates

Encorafenib is a strong inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in loss of efficacy of these agents. If the coadministration of narrow therapeutic index CYP3A4 substrates cannot be avoided, adjust the dose of these substrates in accordance with their approved SmPC.

Encorafenib is an inhibitor of UGT1A1. Concomitant agents that are substrates of UGT1A1 (e.g. raltegravir, atorvastatin, dolutegravir) may have increased exposure and should be therefore administered with caution.

Effect of encorafenib on binimetinib

While encorafenib is a relatively potent reversible inhibitor of UGT1A1, no differences in binimetinib exposure have been observed clinically when binimetinib was co-administered with encorafenib.

Transporter substrates

In vivo, encorafenib is an inhibitor of OATP1B1, OATP1B3 and/or BCRP. Coadministration of encorafenib with OATP1B1, OATP1B3 or BCRP substrates (such as rosuvastatin, atorvastatin, methotrexate) can result in increased concentrations (see section 5.2).

In vitro, encorafenib potentially inhibits a number of other transporters. Agents that are substrates of renal transporters OAT1, OAT3, OCT2 (such as furosemide, penicillin) or agents that are substrates of the hepatic transporters OCT1 (such as, bosentan) or substrates of P-gp (e.g. posaconazole) may also have increased exposure.

Therefore, these agents, substrates of transporters should be co-administered with caution.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females

Women of childbearing potential must use effective contraception during treatment with encorafenib and for at least 1 month following the last dose. Encorafenib may decrease the efficacy of hormonal contraceptives (see section 4.5). Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (*e.g.* condom) during treatment with encorafenib and for at least 1 month following the last dose.

Pregnancy

There are no data from the use of encorafenib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Encorafenib is not recommended during pregnancy and in women of childbearing potential not using contraception. If encorafenib is used during pregnancy or if the patient becomes pregnant while taking encorafenib, the patient should be informed of the potential hazard to the foetus.

Breast-feeding

It is unknown whether encorafenib or its metabolites are excreted in human milk. A risk to the breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue encorafenib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

There are no data on the effects of encorafenib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential (see section 5.3). As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis.

4.7 Effects on ability to drive and use machines

Encorafenib has minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machines (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of safety profile

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) has been evaluated in the integrated safety population (ISP) of 372 patients including patients with BRAF V600 mutant unresectable or metastatic melanoma and BRAF V600E mutant advanced NSCLC (hereafter referred to as the Combo 450 ISP). In Combo 450 ISP, 274 patients received the combination for the treatment of BRAF V600 mutant unresectable or metastatic melanoma (in two Phase II studies (CMEK162X2110 and CLGX818X2109) and one Phase III study (CMEK162B2301, Part 1)), and 98 patients received the combination for the treatment of BRAF V600E mutant advanced NSCLC (in one Phase II study (ARRAY-818-202)) (see section 5.1). The most common adverse reactions ($\geq 25\%$) occurring in patients treated with encorafenib administered with binimetinib were fatigue, nausea, diarrhoea, vomiting, abdominal pain, myopathy/muscular disorders, and arthralgia.

The safety of encorafenib (300 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 257 patients with BRAF V600 mutant unresectable or metastatic

melanoma (hereafter referred to as the Combo 300 population), based on the Phase III study (CMEK162B2301, Part 2). The most common adverse reactions ($\geq 25\%$) occurring in patients treated with encorafenib 300 mg administered with binimetinib were fatigue, nausea and diarrhoea.

The encorafenib single agent (300 mg orally once daily) safety profile is based on data from 217 patients with unresectable or metastatic BRAF V600-mutant melanoma (hereafter referred to as the pooled encorafenib 300 population). The most common adverse drug reactions (ADRs) ($\geq 25\%$) reported with encorafenib 300 were hyperkeratosis, alopecia, PPES, fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and pruritus.

The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (dosed as per its SmPC) was evaluated in 216 patients with BRAF V600E-mutant metastatic colorectal cancer, based on the phase III study ARRAY-818-302. The most common ADRs ($>25\%$) reported in this population were: fatigue, nausea, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/musculoskeletal pain, decreased appetite, rash and vomiting.

The rate of all study drug discontinuation due to any adverse reaction was 1.9 % in patients treated with encorafenib 300 mg in combination with cetuximab.

The safety of encorafenib (300 mg orally once daily) in combination with cetuximab and FOLFOX was evaluated in 259 patients with BRAF V600E-mutant metastatic colorectal cancer, based on the study C4221015 – BREAKWATER (hereafter referred to as the pooled EC+FOLFOX population, i.e. all patients who received encorafenib and cetuximab (EC)+FOLFOX in the different portions of the study). The most common ADRs ($\geq 25\%$) reported in this population were: neuropathy peripheral, neutropenia, nausea, fatigue, anaemia, diarrhoea, vomiting, decreased appetite, rash, thrombocytopenia, abdominal pain, haemorrhage, arthralgia/musculoskeletal pain, pyrexia, constipation, mucosal inflammation and infection.

The rate of all study drug discontinuation due to any adverse reaction was 3.5 % in patients treated with encorafenib 300 mg in combination with cetuximab and FOLFOX.

Tabulated list of adverse reactions

Adverse reactions are listed below by MedDRA body system organ class and the following frequency convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions

Frequency	Encorafenib single agent 300 mg (n = 217)	Encorafenib 450 mg in combination with binimetinib (n = 372)	Encorafenib 300 mg in combination with cetuximab (n = 216)	Encorafenib 300 mg in combination with cetuximab and FOLFOX (n = 259)
Neoplasms benign, malignant and unspecified				
Very common	Skin papilloma* Melanocytic naevus		Melanocytic naevus	
Common	cuSCC ^a New Primary Melanoma*	cuSCC ^a Skin papilloma*	cuSCC ^a Skin papilloma* New Primary Melanoma*	Melanocytic naevus Skin papilloma* Basal cell carcinoma cuSCC ^a
Uncommon	Basal cell carcinoma	Basal cell carcinoma*	Basal cell carcinoma*	New Primary Melanoma*
Blood and lymphatic system disorders				

Very common		Anaemia		Neutropenia* Anaemia* Thrombocytopenia* Leukopenia*
Immune system disorders				
Very common				Hypersensitivity ^b
Common	Hypersensitivity ^b	Hypersensitivity ^b	Hypersensitivity ^b	
Metabolism and nutrition disorders				
Very common	Decreased appetite		Decreased appetite	Decreased appetite Hypokalaemia Hypomagnesaemia Hypoalbuminaemia*
Not known		Tumour lysis syndrome		
Psychiatric disorders				
Very common	Insomnia		Insomnia	Insomnia*
Nervous system disorders				
Very common	Headache* Neuropathy peripheral* Dysgeusia*	Neuropathy peripheral* Dizziness* Headache*	Neuropathy peripheral* Headache*	Neuropathy peripheral ⁿ Dysgeusia* Headache*
Common	Facial paresis ^c	Dysgeusia*	Dizziness* Dysgeusia	Dizziness*
Uncommon		Facial paresis ^c		
Eye disorders				
Very common		Visual impairment* RPED*		
Common		Uveitis*		
Uncommon	Uveitis*			
Cardiac disorders				
Common	Supraventricular tachycardia ^d	LVD ^h	Supraventricular tachycardia ^d	Supraventricular tachycardia ^d
Vascular disorders				
Very common		Haemorrhage ⁱ Hypertension*	Haemorrhage ⁱ	Haemorrhage ⁱ
Common		VTE ^j		
Gastrointestinal disorders				
Very common	Nausea Vomiting* Constipation	Nausea Vomiting* Constipation Abdominal pain* Diarrhoea*	Nausea Vomiting* Constipation Abdominal pain* Diarrhoea*	Nausea Diarrhoea* Vomiting* Abdominal pain* Constipation Mucosal inflammation*
Common		Colitis ^k		
Uncommon	Pancreatitis*	Pancreatitis*	Pancreatitis*	Pancreatitis*

Skin and subcutaneous tissue disorders				
Very common	PPES Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia* Erythema ^e Skin hyperpigmentation*	Hyperkeratosis* Rash* Dry skin* Pruritus* Alopecia*	Dermatitis acneiform* Rash* Dry skin* Pruritus*	Rash* Skin hyperpigmentation* Dermatitis acneiform* Dry skin* Alopecia PPES Pruritus
Common	Dermatitis acneiform* Skin exfoliation ^f Photosensitivity*	Dermatitis acneiform* PPES Erythema* Panniculitis* Photosensitivity*	Skin hyperpigmentation PPES Hyperkeratosis* Alopecia Erythema ^e	Erythema Hyperkeratosis* Skin exfoliation
Uncommon			Skin exfoliation ^f	
Musculoskeletal and connective tissue disorders				
Very common	Arthralgia* Myalgia ^g Pain in extremity Back pain	Arthralgia* Myopathy/Muscular disorder ^l Pain in extremity Back pain*	Arthralgia/Musculoskeletal pain* Myopathy/Muscular disorder* Pain in extremity Back pain	Arthralgia/Musculoskeletal pain* Myopathy/Muscular disorder ^l Back pain*
Common	Arthritis*			Pain in extremity*
Uncommon		Rhabdomyolysis		
Renal and urinary disorders				
Common	Renal failure*	Renal failure*	Renal failure*	Renal failure*
General disorders and administration site conditions				
Very common	Fatigue* Pyrexia*	Fatigue* Pyrexia* Peripheral oedema ^m	Fatigue* Pyrexia*	Fatigue* Pyrexia*
Infections and infestations				
Very common				Infections ^o
Common				Upper respiratory tract infection* Sepsis*

Investigations				
Very common	Gamma-glutamyl transferase (GGT) increased*	Blood creatine phosphokinase increased Gamma-glutamyl transferase (GGT) increased* Transaminase increased*		Lipase increased* Weight decreased Transaminase increased*
Common	Transaminase increased* Blood creatinine increased* Lipase increased	Blood alkaline phosphatase increased Blood creatinine increased* Amylase increased Lipase increased	Blood creatinine increased* Transaminase increased*	Blood creatinine increased* Amylase increased*
Uncommon	Amylase increased		Amylase increased Lipase increased	

*composite terms which included more than one preferred term

^a includes keratoacanthoma, squamous cell carcinoma and squamous cell carcinoma of skin

^b includes, but not limited to, angioedema, anaphylactic reaction, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis and urticaria

^c includes facial nerve disorder, facial paralysis, facial paresis, Bell's palsy

^d includes but not limited to extrasystoles, supraventricular tachycardia, atrial tachycardia and sinus tachycardia

^e includes erythema, generalised erythema, plantar erythema

^f includes dermatitis exfoliative, skin exfoliation, exfoliative rash

^g includes myalgia, muscle fatigue, muscle injury, muscle spasm, muscle weakness

^h includes left ventricular dysfunction, ejection fraction decreased, cardiac failure and ejection fraction abnormal

ⁱ includes haemorrhage at various sites including, but not limited to, cerebral haemorrhage, intracranial haemorrhage, vaginal haemorrhage, heavy menstrual bleeding, intermenstrual bleeding, haematochezia, epistaxis, haemoptysis, haemothorax, gastrointestinal haemorrhage and haematuria

^j includes, but not limited to, pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis, thrombophlebitis superficial, thrombosis, phlebitis, superior vena cava syndrome, mesenteric vein thrombosis and vena cava thrombosis

^k includes colitis, colitis ulcerative, enterocolitis and proctitis

^l includes, but not limited to, myalgia, muscular weakness, muscle spasm, muscle injury, myopathy, myositis

^m includes, but not limited to, fluid retention, peripheral oedema, localised oedema, generalised oedema and swelling

ⁿ includes but not limited to cold dysaesthesia, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral sensory neuropathy, polyneuropathy

^o includes but not limited to urinary tract infection, gastroenteritis, peritonitis, cellulitis, abdominal infection, gastrointestinal infection, infection, lower respiratory tract infection, viral and bacterial pneumonia, viral infection

When encorafenib was used at a dose of 300 mg once daily in combination with binimetinib 45 mg twice daily (Combo 300) in study CMEK162B2301-Part 2, the frequency category was lower compared to the pooled Combo 450 population for the following adverse reactions: anaemia, peripheral neuropathy, haemorrhage, hypertension, pruritus (common); and colitis, increased amylase and increased lipase (uncommon).

Description of selected adverse reactions

Cutaneous malignancies

Cutaneous squamous cell carcinoma

Melanoma and NSCLC

In the Combo 450 ISP, cuSCC including keratoacanthomas was observed in 3.0% (11/372) of patients. The median time to onset of the first event of cuSCC (all grades) was 6.5 months (range 1.0 to 22.8 months).

In the pooled encorafenib 300 population, cuSCC was reported in 7.4% (16/217) patients. For patients in the Phase III study (CMEK162B2301) who developed cuSCC, the median time to onset of the first event of cuSCC (all grades) was 2.3 months (range 0.3 to 12.0 months).

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, cuSCC including keratoacanthoma was observed in 1.4% (3/216) of patients. The times to first event of cuSCC (all grades) were 0.5, 0.6 and 3.6 months for these 3 patients.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, cuSCC including keratoacanthoma was observed in 1.2% (3/259) of patients. The times to first event of cuSCC (all grades) were 1.9, 2.9 and 6.1 months for these 3 patients. No treatment discontinuation was reported.

New primary melanoma

Melanoma

In the pooled encorafenib 300 population, new primary melanoma events occurred in 4.1% of patients (9/217) and was reported as Grade 1 in 1.4% (3/217) of patients, Grade 2 in 2.1% (4/217) of patients, Grade 3 in 0.5% (1/217) of patients and Grade 4 in 0.5% (1/217) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, new primary melanoma events occurred in 1.9% of patients (4/216) and were reported as Grade 2 in 0.9% (2/216) of patients and Grade 3 in 0.9% (2/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, new primary melanoma events occurred in 0.8% of patients (2/259) and all were reported as Grade 3. Dose interruptions or dose reductions were required in 0.4% (1/259) of patients. No treatment discontinuation was reported.

Ocular events

Melanoma and NSCLC

In the Combo 450 population, uveitis was reported in 3.5% (13/372) of patients, and was Grade 1 in 0.5% (2/372), Grade 2 in 2.7% (10/372) and Grade 3 in 0.3% (1/372). Visual impairment, including blurred vision and reduced visual acuity, occurred in 23.1% (86/372) of patients. Uveitis and visual impairment were generally reversible.

RPED occurred in 22.3% (83/372) of patients, most of them had Grade 1-2 and 1.6% (6/372) had Grade 3 events.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, RPED was observed in 12.5% (32/257) of patients with 0.4% (1/257) Grade 4 event.

Left ventricular dysfunction

LVD was reported when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Haemorrhage

Melanoma and NSCLC

Haemorrhagic events were observed in 16.7% (62/372) of patients in the Combo 450 ISP. Most events were Grade 1 or 2: 13.2% (49/372), and 3.5% (13/372) were Grade ≥ 3 . Few patients required dose interruptions or dose reductions (2.4% or 9/372). Haemorrhagic events led to discontinuation of treatment in 0.8% (3/372) of patients. The most frequent haemorrhagic events were haematuria in 2.7% (10/372) of patients, haematochezia in 2.7% (10/372) and rectal haemorrhage in 2.2% (8/372) of patients. Fatal gastric ulcer haemorrhage, with multiple organ failure as a concurrent cause of death, occurred in one patient. Cerebral haemorrhage/intracranial haemorrhage was reported in 1.6% (6/372) of patients, with fatal outcome in 4 patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, haemorrhagic events were observed in 6.6% (17/257) of patients and were Grade 3-4 in 1.6% (4/257) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

Haemorrhagic events were observed in 21.3% (46/216) of patients treated with encorafenib 300 mg in combination with cetuximab; 1.4% (3/216) of patients were Grade 3 events and one fatal case was reported. Dose interruptions or dose reductions were required in 1.9% (4/216) of patients. Haemorrhagic events led to treatment discontinuation in 1 patient (0.5%).

The most frequent haemorrhagic events were epistaxis in 6.9% (15/216) of patients, haematochezia in 2.8% (6/216), rectal haemorrhage in 2.8% (6/216) of patients and haematuria in 2.8% (6/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

Haemorrhagic events were observed in 32.8% (85/259) of the pooled EC+FOLFOX population; 1.5% (4/259) of patients were Grade 3 events and 0.8% (2/259) of patients were Grade 4 events. Dose interruptions or dose reductions were required in 3.9% (10/259) of patients. No treatment discontinuation was reported.

The most frequent haemorrhagic events were epistaxis in 18.5% (48/259) of patients, haematuria in 4.2% (11/259), gingival bleeding in 3.9% (10/259), and rectal haemorrhage and hemorrhoidal haemorrhage in 3.5% each (9/259) of patients.

Hypertension

Hypertension was reported when encorafenib was used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Venous thromboembolism

VTE was reported when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Pancreatitis

Melanoma and NSCLC

In the Combo 450 ISP, pancreatic enzyme elevation, mostly asymptomatic, was reported. Amylase and lipase elevations were reported in 4.0% (15/372) and 7.8% (29/372) of patients, respectively. Pancreatitis was reported in 0.8% (3/372) of patients. All 3 patients experienced Grade 3 events. Pancreatitis led to dose interruption in 0.3% (1/372) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In the population treated with encorafenib 300 mg in combination with cetuximab, pancreatitis grade 3 with lipase and amylase increased events were reported in 1 patient (0.5%) and led to dose interruption.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, increased lipase events (mostly asymptomatic) were reported in 23.6% of patients. Pancreatitis Grade 3 was reported in 2 patients (0.8%) with lipase increased events reported for one patient. Dose interruption was reported for both patients and treatment discontinuation for one patient.

Dermatologic reactions

Rash

Melanoma and NSCLC

In the Combo 450 ISP, rash occurred in 20.4% (76/372) of patients. Most events were mild, with Grade 3 or 4 events reported in 1.1 (4/372) of patients. Rash led to discontinuation in 0.8% (3/372) patients and to dose interruption or dose modification in 2.4% (9/372) of patients.

In the pooled encorafenib 300 population, rash was reported in 43.3% (94/217) of patients. Most events were mild, with Grade 3 or 4 events reported in 4.6% (10/217) of patients. Rash led to discontinuation in 0.5% (1/217) of patients and to dose interruption or dose modification in 7.4% (16/217) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, rash occurred in 30.6% (66/216) of patients. Most events were mild, with Grade 3 event reported in 0.5% (1/216) of patients. Rash led to dose interruption in 0.5% (1/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, rash occurred in 35.9% (93/259) of patients. Most events were mild, with Grade 3 event reported in 1.2% (3/259) of patients. Rash led to treatment discontinuation in 0.8% (2/259) of patients and led to dose interruption or reduction in 4.2% (11/259) of patients.

Palmar-plantar erythrodysesthesia syndrome (PPES)

Melanoma and NSCLC

PPES was reported in 5.1% (19/372) of patients in the Combo 450 ISP. All the PPES adverse reactions were either Grade 1 (2.7%) or Grade 2 (2.4%). Dose interruption or dose modification occurred in 1.1% (4/372) of patients.

In the Combo 300 arm in Part 2 of the pivotal study, PPES was observed in 3.9% (10/257) of patients with Grade 3 reported in 0.4% (1/257) of patients.

In the pooled encorafenib 300 population, PPES was reported in 51.6% (112/217) of patients. Most events were mild-moderate: Grade 1 in 12.4% (27/217) of patients, Grade 2 in 26.7% (58/217) and Grade 3 in 12.4% (27/217) of patients. PPES led to discontinuation in 4.1% (9/217) of patients and to dose interruption or dose modification in 23.0% (50/217) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In the population treated with encorafenib 300 mg in combination with cetuximab, PPES was reported in 5.1% (11/216) of patients. Most of PPES adverse reactions were Grade 1 in 3.7 % (8/216). Grade 2 events were reported in 0.9% (2/216) of patients, and Grade 3 in 0.5% (1/216) of patients. No dose interruption, dose modification or treatment discontinuation was required.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, PPES was reported in 15.8% (41/259) of patients. Most of the events were Grade 1 or 2, and 2.7% (7/259) were Grade 3 events. PPES led to treatment discontinuation in 0.4% (1/259) of patients and led to dose interruption or reduction in 3.5% (9/259) of patients.

Dermatitis acneiform

Melanoma and NSCLC

Dermatitis acneiform was reported when encorafenib is used in combination with binimetinib (see section 4.8 of binimetinib SmPC).

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, dermatitis acneiform occurred in 33.3% (72/216) of patients and was mostly Grade 1 (25.5% (55/216) of patients), or 2 (6.9% (15/216) of patients). Dose reduction or interruption was reported in 2.3 % (5/216) of patients. No treatment discontinuation was reported. Dermatitis acneiform was generally reversible.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, dermatitis acneiform occurred in 22.4% (58/259) of patients. Most of the events were Grade 1 or 2, and 0.8% (2/259) were Grade 3 events. Dose reduction or interruption was reported in 1.9 % (5/259) of patients. No treatment discontinuation was reported.

Photosensitivity

Melanoma and NSCLC

In the Combo 450 ISP, photosensitivity was observed in 4.3% (16/372) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.3% (1/372) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.3% (1/372) of patients.

In the pooled encorafenib 300 population, photosensitivity was reported in 4.1% (9/217) of patients. All events were Grade 1-2. No event required discontinuation, dose modification or interruption.

Facial paresis

Melanoma and NSCLC

In the Combo 450 ISP, facial paresis occurred in 0.8% (3/372) of patients including Grade 3 in 0.3% (1/372) of patients. The events were reversible, and no event led to treatment discontinuation. Dose interruption or modification was reported in 0.3% (1/372) of patients.

In the pooled encorafenib 300 population, facial paresis was observed in 7.4% (16/217) of patients. Most events were mild-moderate: Grade 1 in 2.3% (5/217); Grade 2 in 3.7% (8/217) and Grade 3 in 1.4% (3/217) of patients. The median time to onset of the first event of facial paresis was 0.3 months (range 0.1 to 12.1 months). Facial paresis was generally reversible and led to treatment discontinuation in 0.9% (2/217). Dose interruption or modification was reported in 3.7% (8/217) and symptomatic treatment including corticosteroids was reported in 5.1% (11/217) of patients.

CK elevation and rhabdomyolysis

CK elevation and rhabdomyolysis occurred when encorafenib is used in combination with binimetinib in melanoma and NSCLC patients (see section 4.8 of binimetinib SmPC).

Renal dysfunction

Melanoma and NSCLC

In the Combo 450 ISP, mild, mostly Grade 1, asymptomatic blood creatinine elevation was noted in 9.4% (35/372) of patients treated with the Combo 450. The incidence of Grade 3 or 4 elevation was 0.8% (3/372). Renal failure events, including acute kidney injury, renal failure and renal impairment, were reported in 3.5% (13/372) patients treated with encorafenib and binimetinib with Grade 3 or 4 events in 1.9% (7/372) of patients. Renal failure was generally reversible with dose interruption, rehydration and other general supportive measures.

Colorectal cancer

Encorafenib and cetuximab combination

Blood creatinine elevation was reported in 2.8% (6/216) of patients treated with encorafenib 300 mg in combination with cetuximab. All were mild except one event of Grade 4. Renal failure events were

Grade 3 or 4 and reported as acute kidney injury in 1.9 % (4/216) of patients and renal failure in 0.5% (1/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

Blood creatinine elevation was reported in 3.9% (10/259) of the pooled EC+FOLFOX population. All events were either Grade 1 (2.7% (7/259) of patients) or Grade 2 (1.2% (3/259) of patients).

Renal failure, including acute kidney injury and renal impairment, was reported in 3.5% (9/259) of patients (Grade 3 events in 1.2% of patients and Grade 4 events in 0.4% of patients). Renal failure events led to interruption or dose reduction in 2.7% of patients and were resolved in 90% of cases. No treatment discontinuation was reported.

Liver laboratory abnormality

Melanoma and NSCLC

The incidences of liver laboratory abnormalities reported in the Combo 450 ISP are listed below:

- Increased transaminases: 16.4% (61/372) overall – 6.5% (24/372) Grade 3
- Increased GGT: 11.3% (42/372) overall – 6.7% (25/372) Grade 3-4

In Study CMEK162B2301-Part 2, in the Combo 300 arm, the incidence of liver laboratory abnormalities was:

- Increased transaminases: 13.2% (34/257) overall – 5.4% (14/257) Grade 3-4
- Increased GGT: 14.0% (36/257) overall – 4.7% (12/257) Grade 3-4

Colorectal cancer

Encorafenib and cetuximab combination

The incidence of increased transaminases in patients treated with encorafenib 300 mg in combination with cetuximab was 8.8% (19/216) of patients, with Grade 3 in 1.4% (3/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

The incidence of increased transaminases reported in the pooled EC+FOLFOX population was 17.0% (44/259) of patients, with Grade 3 events in 1.5% (4/259) of patients.

Gastrointestinal disorders

Melanoma and NSCLC

In the Combo 450 ISP, diarrhoea was observed in 41.7% (155/372) of patients and was Grade 3-4 in 3.8% (14/372) patients. Diarrhoea led to treatment discontinuation in 0.8% of patients and to dose interruption or dose modification in 8.1% of patients.

Constipation occurred in 24.7% (92/372) of patients and was Grade 1 or 2. Abdominal pain was reported in 28.5% (106/372) of patients and was Grade 3 in 2.2% (8/372) patients. Nausea occurred in 46.0% (171/372) with Grade 3 observed in 3.0% (11/372) of patients. Vomiting occurred in 31.2% (116/372) of patients with Grade 3 reported in 1.9% (7/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, nausea was observed in 27.2% (70/257) of patients and was Grade 3 in 1.6% (4/257) of patients. Vomiting occurred in 15.2% (39/257) of patients with Grade 3 reported in 0.4% (1/257) of patients. Diarrhoea occurred in 28.4% (73/257) of patients with Grade 3 reported in 1.6% (4/257) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, diarrhoea was observed in 38.4% (83/216) of patients and was Grade 3 in 2.8% (6/216) of patients. Diarrhoea led to treatment discontinuation in 0.5% (1/216) of patients and to dose interruption or dose modification in 3.7% (8/216) of patients.

Abdominal pain was reported in 36.6% (79/216) of patients and was Grade 3 in 5.1% (11/216) of patients. Nausea occurred in 38.0% (82/216) of patients with Grade 3 observed in 0.5% (1/216) of patients. Vomiting occurred in 27.3% (59/216) of patients with Grade 3 reported in 1.4 % (3/216) of patients. Constipation occurred in 18.1% (39/216) of patients and was Grade 1 or 2.

Gastrointestinal disorders were typically managed with standard therapy.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, diarrhoea was observed in 41.3% (107/259) of patients and was Grade 3 in 1.9% (5/259) of patients. Diarrhoea led to treatment discontinuation in 1.2% (3/259) of patients and to dose interruption or dose modification in 8.9% (23/259) of patients.

Abdominal pain was reported in 32.8% (85/259) of patients and was Grade 3 in 5.4% (14/259) of patients. Nausea occurred in 56.0% (145/259) of patients with Grade 3 observed in 2.7 % (7/259) of patients. Vomiting occurred in 36.7% (95/259) of patients with Grade 3 reported in 3.9% (10/259) of patients. Constipation occurred in 27.0% (70/259) of patients with Grade 3 observed in 0.4% (1/259) of patients.

Gastrointestinal disorders were typically managed with standard therapy.

Anaemia

Melanoma and NSCLC

In the Combo 450 ISP, anaemia was reported in 23.1% (86/372) of patients; 7.0% (26/372) patients had a Grade 3 or 4. No patients discontinued treatment due to anaemia, 3.2% (12/372) required dose interruption or dose modification.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, anaemia was observed in 9.7% (25/257) of patients with Grade 3-4 reported in 2.7% (7/257) patients.

Colorectal cancer

Encorafenib and cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, anaemia was reported in 43.6% (113/259) of patients; 14.3% (37/259) patients had a Grade 3. Anaemia led to treatment discontinuation in 2.3% (6/259) of patients and to dose interruption or dose modification in 13.9% (36/259) of patients.

Headache

Melanoma and NSCLC

In the Combo 450 ISP, headache occurred in 18.8% (70/372) of patients, including Grade 3 in 1.1% (4/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, headache was reported in 12.1% (31/257) of patients and was Grade 3 in 0.4% (1/257) of patients.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, headache occurred in 20.4% (44/216) of patients and was Grade 1 or 2.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, headache occurred in 15.1% (39/259) of patients and 0.4% (1/259) of case was reported as Grade 3. Dose interruptions or dose reductions were required in 0.4% (1/259) of patients. No treatment discontinuation was reported.

Fatigue

Melanoma and NSCLC

In the Combo 450 ISP, fatigue occurred in 48.1% (179/372) of patients including Grade 3 or 4 in 4.3% (16/372) of patients.

In Study CMEK162B2301-Part 2, in the Combo 300 arm, fatigue was observed in 33.5% (86/257) of patients with 1.6% (4/257) Grade 3-4 events.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab, fatigue was reported in 56.9% (123/216) of patients including Grade 3 in 7.9% (17/216) of patients.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population, fatigue was reported in 54.1% (140/259) of patients including Grade 3 events in 6.6% (17/259) of patients. Fatigue led to treatment discontinuation in 3.5% (9/259) of patients and to dose interruption or dose modification in 16.6% (43/259) of patients.

Special populations

Elderly

Melanoma and NSCLC

In patients treated with Combo 450 ISP (n = 372), 230 patients (61.8%) were <65 years old, 107 patients (28.8%) were 65 -74 years old and 35 patients (9.4%) were aged > 75. No overall differences in safety or efficacy were observed between elderly patients (≥ 65) and younger patients except diarrhoea and pruritus that were more frequently reported in elderly patients.

In the age subgroup of patients aged ≥ 75 years, Grade ≥3 adverse reactions (62.9% vs 47.5%), adverse reactions (all grades) requiring dose modification of any study drug (60.0% vs 48.1%) or leading to treatment discontinuation (25.7% vs 7.4%) were more frequently reported than in patients <75 years. The most common adverse reactions reported with a higher incidence in patients aged ≥ 75 years compared to patients aged < 75 years included fatigue, nausea, diarrhoea, vomiting and anaemia.

Colorectal cancer

Encorafenib and cetuximab combination

In patients treated with encorafenib 300 mg in combination with cetuximab (n=216), 134 patients (62 %) were < 65 years old, 62 patients (28.7%) were 65-74 years old, and 20 patients (9.3%) were aged ≥ 75. The most common adverse reactions reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included fatigue, decreased appetite, and haemorrhage.

Encorafenib with cetuximab and FOLFOX combination

In the pooled EC+FOLFOX population (n=259), 166 patients (64.1 %) were < 65 years old, 93 patients (35.9%) were 65 years and older. The most common adverse reactions reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included neutropenia, anaemia, infection, weight decreased and hypomagnesaemia.

In the colorectal cancer population, due to a very small number of patients treated in the age subgroup of patients aged ≥ 75 years, differences in the incidence of adverse reactions compared to patients aged < 75 years could not be assessed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Symptoms

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinemia) was observed in 3 out of 14 patients. The highest administered dose occurred as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose

1200 mg). Adverse reactions reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved.

Management

There is no specific treatment for overdose.

Since encorafenib is moderately bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose with encorafenib. There is no known antidote for encorafenib. In the event of an overdose, encorafenib treatment should be interrupted and renal function must be monitored as well as adverse reactions. Symptomatic treatment and supportive care should be provided as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EC03

Mechanism of action

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC_{50}) of encorafenib against BRAF V600E, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, encorafenib inhibits *in vitro* and *in vivo* BRAF V600E, D and K mutant melanoma cell growth and BRAF V600E mutant colorectal cancer cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Combination with binimetinib

Encorafenib and binimetinib (a MEK inhibitor, see section 5.1 of binimetinib SmPC) both inhibit the MAPK pathway, resulting in higher anti-tumour activity, compared to treatment with either drug alone.

Combination with cetuximab with or without FOLFOX

One of the main mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors has been identified as the re-activation of EGFR with bypassing signal transduction via BRAF. Combinations of a BRAF inhibitor, *e.g.* encorafenib and agents targeting EGFR, *e.g.* cetuximab have shown to improve anti-tumour efficacy in non-clinical models. The addition of a cytostatic agent, *e.g.* 5-fluorouracil and a cytotoxic agent, *e.g.* oxaliplatin, have shown to improve anti-tumour efficacy in clinical studies.

Clinical efficacy and safety

BRAF V600 Mutant Unresectable or Metastatic Melanoma

The safety and efficacy of encorafenib in combination with binimetinib were evaluated in a 2-part Phase III, randomised (1:1:1) active-controlled, open-label, multicentre study in patients with unresectable or metastatic BRAF V600 E or K mutant melanoma (Study CMEK162B2301), as detected using a BRAF assay. Patients had histologically confirmed cutaneous or unknown primary melanoma but those with uveal or mucosal melanoma were excluded. Patients were permitted to receive prior adjuvant therapy and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior treatment with BRAF/ MEK inhibitors was not allowed.

Study CMEK162B2301, part 1

In Part 1, patients in the study were randomised to receive encorafenib 450 mg orally daily and binimetinib 45 mg orally twice daily (Combo 450, n = 192), encorafenib 300 mg orally daily (Enco 300, n = 194), or vemurafenib 960 mg orally twice daily (hereafter referred to as Vem, n = 191). Treatment continued until disease progression or unacceptable toxicity. Randomisation was stratified

by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, vs IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and prior immunotherapy for unresectable or metastatic disease (yes vs no).

The primary efficacy outcome measure was progression-free survival (PFS) of Combo 450 compared with vemurafenib as assessed by a blinded independent review committee (BIRC). PFS as assessed by investigators (investigator assessment) was a supportive analysis. An additional secondary endpoint included PFS of Combo 450 compared with Enco 300. Other secondary efficacy comparisons between Combo 450 and either vemurafenib or Enco 300 included overall survival (OS), objective response rate (ORR), duration of response (DoR) and disease control rate (DCR) as assessed by BIRC and by investigator assessment.

The median age of patients was 56 years (range 20-89), 58% were male, 90% were Caucasian, and 72% of patients had baseline ECOG performance status of 0. Most patients had metastatic disease (95%) and were Stage IVM1c (64%); 27% of patients had elevated baseline serum lactate dehydrogenase (LDH), and 45% of patients had at least 3 organs with tumour involvement at baseline and 3.5% had brain metastases. 27 patients (5%) had received prior checkpoint inhibitors (anti-PD1/PDL1 or ipilimumab) (8 patients in Combo 450 arm (4%); 7 patients in vemurafenib arm (4%); 12 patients in Enco 300 arm (6%) including 22 patients in the metastatic setting (6 patients in Combo 450 arm; 5 patients in vemurafenib arm; 11 patients in Enco 300 arm) and 5 patients in the adjuvant setting (2 patients in Combo 450 arm; 2 patients in vemurafenib arm; 1 patient in Enco 300 arm).

The median duration of exposure was 11.7 months in patients treated with Combo 450, 7.1 months in patients treated with Enco 300 and 6.2 months in patients treated with vemurafenib. The median relative dose intensity (RDI) for Combo 450 was 100% for encorafenib and 99.6% for binimetinib; the median RDI was 86.2% for Enco 300 and 94.5% for vemurafenib.

Part 1 of Study CMEK162B2301 demonstrated a statistically significant improvement in PFS in the patients treated with Combo 450 compared with patients treated with vemurafenib. Table 6 summarises the PFS and other efficacy results based on central review of the data by a blinded independent radiology committee.

The efficacy results based on investigator assessment were consistent with the independent central assessment. Unstratified subgroup analyses demonstrated point estimates in favour of Combo 450, including LDH at baseline, ECOG performance status and AJCC stage.

Table 6: Study CMEK162B2301, Part 1: Progression-free survival and confirmed overall response results (independent central review)

	Encorafenib + binimetinib N=192 (Combo 450)	Encorafenib N=194 (Enco300)	Vemurafenib N=191 (Vem)
Cut-off date: 19 May 2016			
PFS (primary analysis)			
Number of events (%)	98 (51.0)	96 (49.5)	106 (55.5)
Median, months (95% CI)	14.9 (11.0, 18.5)	9.6 (7.5,14.8)	7.3 (5.6, 8.2)
HR ^a (95% CI) (vs Vem) p-value (stratified log-rank) ^b	0.54 (0.41, 0.71) <0.0001		
HR ^a (95% CI) (vs Vem) Nominal p-value		0.68 (0.52, 0.90) 0.007	

HR ^a (95% CI) (vs Enco 300) p-value (stratified log-rank) ^b	0.75 (0.56,1.00) 0.051		
Confirmed overall responses			
Overall response rate, n (%) (95% CI)	121 (63.0) (55.8, 69.9)	98 (50.5) (43.3, 57.8)	77 (40.3) (33.3, 47.6)
CR, n (%)	15 (7.8)	10 (5.2)	11 (5.8)
PR, n (%)	106 (55.2)	88 (45.4)	66 (34.6)
SD, n (%)	46 (24.0)	53 (27.3)	73 (38.2)
DCR, n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	156 (81.7) (75.4, 86.9)
Duration of response			
Median, months (95% CI)	16.6 (12.2, 20.4)	14.9 (11.1, NE)	12.3 (6.9, 16.9)

CI=Confidence interval; CR=Complete Response; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD; Non-CR/Non-PD applies only to patients without a target lesion who did not achieve CR or have PD); HR=hazard ratio; NE=Not estimable; PFS=progression-free survival; PR=Partial response; SD=stable disease. Vem=vemurafenib.

^a Hazard ratio based on a stratified Cox proportional hazard model

^b Log-rank p-value (2-sided)

Quality of Life (QoL) (cut-off date: 19 May 2016)

The Functional Assessment of Cancer Therapy-Melanoma (FACT-M), the European Organisation for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30) and the EuroQoL-5 Dimension-5 Level examination (EQ-5D-5L) were used to explore patient-reported outcomes (PRO) measures of health-related Quality of Life, functioning, melanoma symptoms, and treatment-related adverse reactions. A definitive 10% deterioration in FACT-M and in EORTC QLQ-C30 was significantly delayed in patients treated with Combo 450 relative to other treatments. The median time to definitive 10% deterioration in the FACT-M score was not reached in the Combo 450 arm and was 22.1 months (95% CI: 15.2, NE) in the vemurafenib arm with a HR for the difference of 0.46 (95% CI: 0.29, 0.72). An analysis of time to definitive 10% deterioration in EORTC QLQ-C30 score provided with similar results.

Patients receiving Combo 450 reported no change or a slight improvement in the mean change from baseline EQ-5D-5L index score at all visits, whilst patients receiving vemurafenib or encorafenib reported decreases at all visits (with statistical significant differences). An evaluation of change over time in score yielded the same trend for EORTC QLQ-C30 and at all visit for FACT-M.

Study CMEK162B2301, part 2

Part 2 of Study CMEK162B2301 was designed to assess the contribution of binimetinib to the encorafenib and binimetinib combination.

The PFS for encorafenib 300 mg orally daily used in combination with binimetinib 45 mg orally twice daily (Combo 300, n = 258) was compared to the PFS for Enco 300 (n = 280, including 194 patients from Part 1 and 86 patients from Part 2). Enrolment in Part 2 started after all Part 1 patients were randomised.

Final efficacy analysis of Study CMEK162B2301, parts 1 and 2 (cut-off date: 31 March 2023)

The final efficacy analysis was consistent with the results of the interim analysis and showed a benefit in OS for Combo 450 over vemurafenib (HR 0.67 [95% CI:0.53,0.84] with median OS of 33.6 months vs 16.9 months). The PFS and ORR (per BIRC) results also confirmed a numerical benefit in favour of Combo 450, with a 7.6 months longer median PFS in the Combo 450 arm as compared to vemurafenib arm, see all detailed final efficacy results in Table 7 and Figures 1 and 2 below.

Moreover, Part 2 final analysis showed a numerical difference in OS for Combo 300 (Part 2) over Enco 300 monotherapy (Parts 1+2) (HR 0.89 [95% CI:0.72,1.09] with median OS of 27.1 months [95% CI:21.6-33.3] vs 22.7 months [95% CI: 19.3-29.3]). The median PFS remained longer in the Combo 300 (Part 2) arm than in the Enco 300 (Parts 1+2) group with median PFS estimates of 12.9 months (95% CI: 10.9, 14.9) and 9.2 months (95% CI: 7.4, 11.1), respectively. The confirmed ORR (per BIRC) was 67.8% (95% CI: 61.8, 73.5) and 51.4% (95% CI 45.4, 57.4) in the Combo 300 (Part 2) and Enco 300 (Parts 1 + 2) arms, respectively. Similar results were observed per Investigator assessment.

Table 7: Study CMEK162B2301 : Final results on PFS, OS and confirmed ORR (cut-off date: 31 March 2023)

	Encorafenib + binimetinib N=192 (Combo 450)	Encorafenib N=194 (Enco 300)	Vemurafenib N=191 (Vem)
Final analysis, cut-off date: 31 March 2023			
PFS (by BIRC)			
Number of events (%)	123 (64.1)	119 (61.3)	121 (63.4)
Median ^a , months (95% CI)	14.9 (11.0, 20.2)	9.6 (7.4, 14.8)	7.3 (5.6, 7.9)
HR ^c (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.51 (0.39, 0.66) <0.0001	0.68 (0.53, 0.88) 0.0017	
HR ^c (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.77 (0.60, 0.99) 0.0214		
OS			
Number of events (%)	139 (72.4)	125 (64.4)	147 (77.0)
Median ^a , months (95% CI)	33.6 (24.4, 39.2)	23.5 (19.6, 33.6)	16.9 (14.0, 24.5)
Survival probability ^b at 1 year % (95%CI)	75.5 (68.8, 81.0)	74.6 (67.6, 80.3)	63.1 (55.7, 69.7)
at 2 years % (95% CI)	57.7 (50.3, 64.3)	49.1 (41.5, 56.2)	43.2 (35.9, 50.2)
at 3 years % (95% CI)	46.5 (39.3, 53.4)	40.9 (33.6, 48.1)	31.4 (24.8, 38.2)
at 5 years % (95% CI)	34.7 (28.0, 41.5)	34.9 (27.9, 42.0)	21.4 (15.7, 27.8)
at 9 years % (95% CI)	26.0 (19.8, 32.5)	27.8 (21.1, 34.8)	18.2 (12.8, 24.3)
HR ^c (95% CI) (vs Vem) Log-rank p-value (1-sided)*	0.67 (0.53, 0.84) 0.0003	0.74 (0.58, 0.94) 0.0063	
HR ^c (95% CI) (vs Enco 300) Log-rank p-value (1-sided)*	0.93 (0.73, 1.19) 0.2821		
Confirmed Best Overall Response (per BIRC)			
Confirmed ORR ^d , n (%) (95% CI)	123 (64.1) (56.8, 70.8)	100 (51.5) (44.3, 58.8)	78 (40.8) (33.8, 48.2)

CR, n (%)	29 (15.1)	17 (8.8)	16 (8.4)
PR, n (%)	94 (49.0)	83 (42.8)	62 (32.5)
SD, n (%)	44 (22.9)	52 (26.8)	71 (37.2)
DCR ^d , n (%) (95% CI)	177 (92.2) (87.4, 95.6)	163 (84.0) (78.1, 88.9)	155 (81.2) (74.8, 86.4)
Duration of Response (per BIRC)			
Median, months (95% CI)	18.6 (12.7, 27.6)	15.5 (11.1, 29.5)	12.3 (6.9, 14.5)
CI=Confidence Interval; CR=Complete Response; PR=Partial response; SD=stable disease; DCR=Disease Control Rate (CR+PR+SD+Non-CR/Non-PD); HR=hazard ratio; ORR=objective response rate (CR+PR); PR and CR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response is first met. ^a Median (time to event) and its 95% CIs are generated by KM estimation with Brookmeyer & Crowley method ^b Survival probability (obtained from the KM survival estimates, Greenwood formula used for CIs) ^c Both Log-rank test and Cox PH model are stratified by IVRS AJCC stage and ECOG Performance status ^d estimated 95% CI are obtained using the exact Clopper-Pearson method *nominal p-value			

Figure 1 Study CMEK162B2301: Kaplan-Meier plot of PFS by BIRC (cut-off date: 31 March 2023)

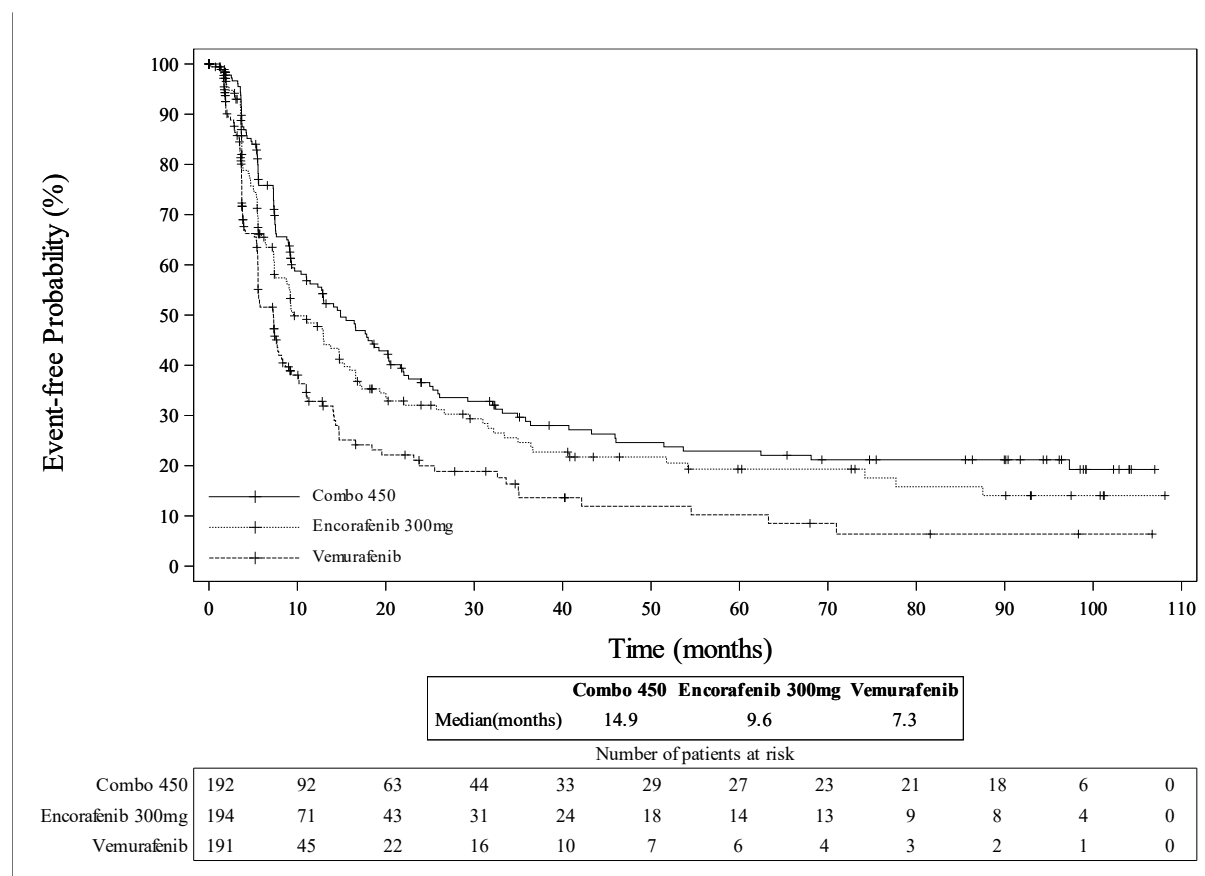
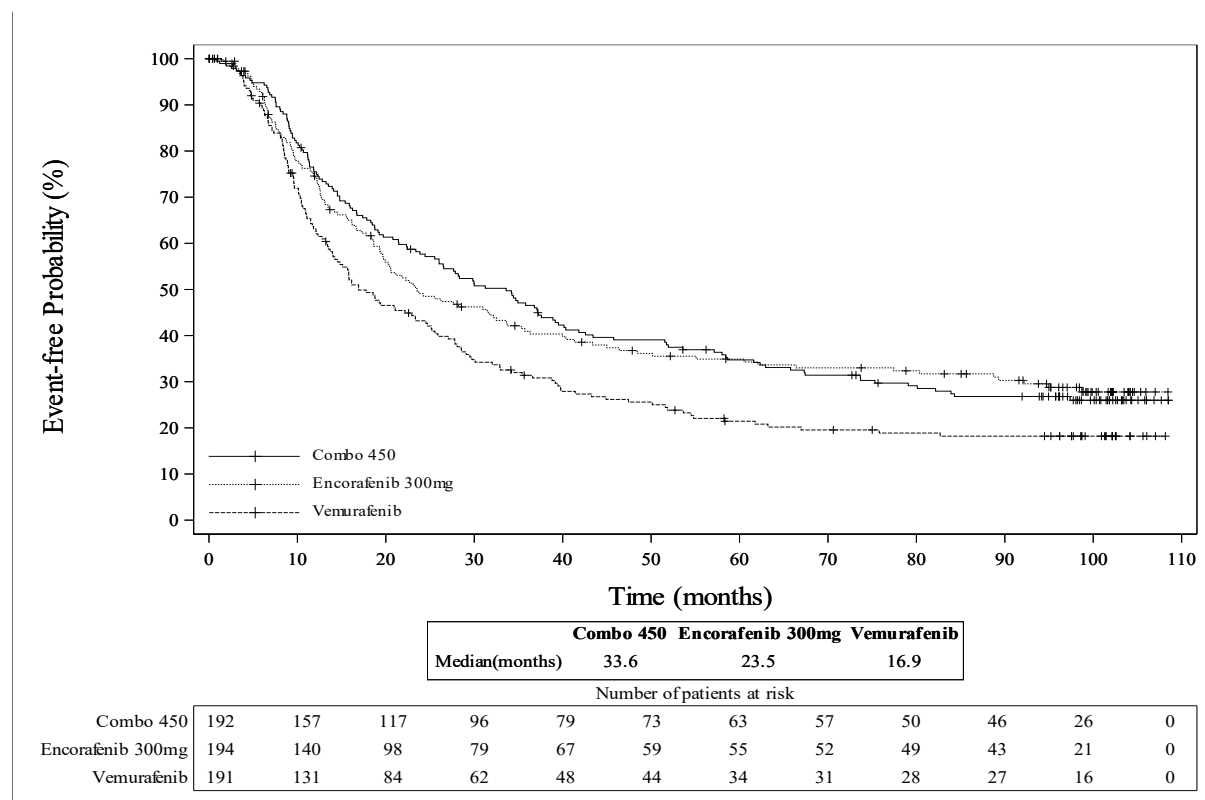


Figure 2 Study CMEK162B2301: Kaplan-Meier plot of OS (cut-off date: 31 March 2023)



BRAF V600E Mutant metastatic colorectal cancer - encorafenib in combination with cetuximab - Study ARRAY-818-302

Encorafenib in combination with cetuximab was evaluated in a randomised, active-controlled, open-label, multicentre trial (ARRAY 818-302 BEACON CRC). Eligible patients were required to have BRAF V600E mutant metastatic colorectal cancer that had progressed after 1 or 2 prior regimens. Enrolled patients were eligible to receive cetuximab per locally approved label with regards to tumour RAS status. Prior use of RAF inhibitors, MEK inhibitors or EGFR inhibitors was prohibited. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status, prior use of irinotecan and cetuximab source.

A total of 665 patients were randomised (1:1:1) to receive encorafenib 300 mg orally daily in combination with cetuximab dosed as per its approved SmPC (n=220), or encorafenib 300 mg orally daily in combination with binimetinib 45 mg orally twice daily and cetuximab dosed as per its approved SmPC (n=224) or Control (irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab, n= 221). Treatment continued until disease progression or unacceptable toxicity.

The efficacy outcome measures were overall survival (OS) and overall response rate (ORR) as assessed by a blinded independent central review committee (BIRC), comparing encorafenib 300 mg in combination with cetuximab versus Control. Other efficacy measures are summarised in Table 8 below.

The median age of patients was 61 years (range 26-91), 47 % were male and 83% were white. 51% of patients had baseline ECOG performance status of 0, and 51% received prior irinotecan. 46.8% of patients had at least 3 organs with tumour involvement at baseline.

The median duration of exposure was 3.2-months in patients treated with encorafenib 300 mg in combination with cetuximab, and 1.4 months in patients treated with irinotecan/cetuximab or FOLFIRI/cetuximab (Control arm). In patients treated with the combination of encorafenib 300 mg and cetuximab, the median relative dose intensity (RDI) was 98% for encorafenib and 93.5% for cetuximab. In the control arm, the median RDI was 85.4% for cetuximab, 75.7% for irinotecan and in the subset of patients who received Folinic acid and 5-FU, the median RDI was 75.2% and 75% respectively.

Encorafenib 300 mg in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR and PFS compared to Control. Efficacy results are summarised in Table 8 and Figures 3.

The efficacy results based on investigator assessment were consistent with the independent central assessment.

Table 8: Study ARRAY-818-302: Efficacy Results

	Encorafenib with cetuximab	Irinotecan with cetuximab or FOLFIRI with cetuximab (Control)
Cut-off date: 11 February 2019 (Primary analysis)		
OS		
Number of patients ^a	220	221
Number of events (%)	93 (42.3)	114 (51.6)
Median, months (95% CI)	8.4 (7.5-11.0)	5.4 (4.8, 6.6)
HR (95% CI) ^{b,c} (vs Control)	0.60 (0.41-0.88)	
p-value ^{b,c}	0.0002	
Median duration of follow-up, months	7.6	7.2

(95% CI)	(6.4, 9.20)	(6.1, 8.1)
ORR (per BIRC)		
Number of patients ^c	113	107
ORR n (%) (95% CI) ^f	23 (20.4) (13.4, 29.0)	2 (1.9) (0.2, 6.6)
P-value ^{b,d,g}	<0.0001	
PFS (per BIRC)		
Number of patients ^a	220	221
Number of events (%)	133 (60.5)	128 (57.9)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.5, 1.7)
HR (95% CI) ^{b,c} P-value ^{b,d}	0.40 (0.30, 0.55) < 0.0001	
Updated analysis, cut-off date: 15 August 2019		
OS		
Number of patients ^a	220	221
Number of events (%)	128 (58.2)	157 (71.0)
Median, months (95% CI)	9.3 (8.0, 11.3)	5.9 (5.1, 7.1)
HR (95% CI) ^b (vs Control) p-value ^{b,d,h}	0.61 (0.48, 0.77) < 0.0001	
Median duration of follow-up, months (95% CI)	12.3 (11.1, 14.1)	12.9 (10.9, 14.6)
PFS (per BIRC)		
Number of patients ^a	220	221
Number of events (%)	167 (75.9)	147 (66.5)
Median PFS, months (95% CI)	4.3 (4.1, 5.5)	1.5 (1.5, 1.9)
HR (95% CI) ^b P-value ^{b,d, h}	0.44 (0.35, 0.55) < 0.0001	

CI = Confidence interval; HR = Hazard ratio; ORR = Overall response rate; OS = Overall survival

^a Randomised Phase 3, Full Analysis Set

^b Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomization

^c Repeated CI derived using Lan DeMets O'Brien-Fleming boundaries associated with the observed information fraction at the interim analysis

^d 1-sided

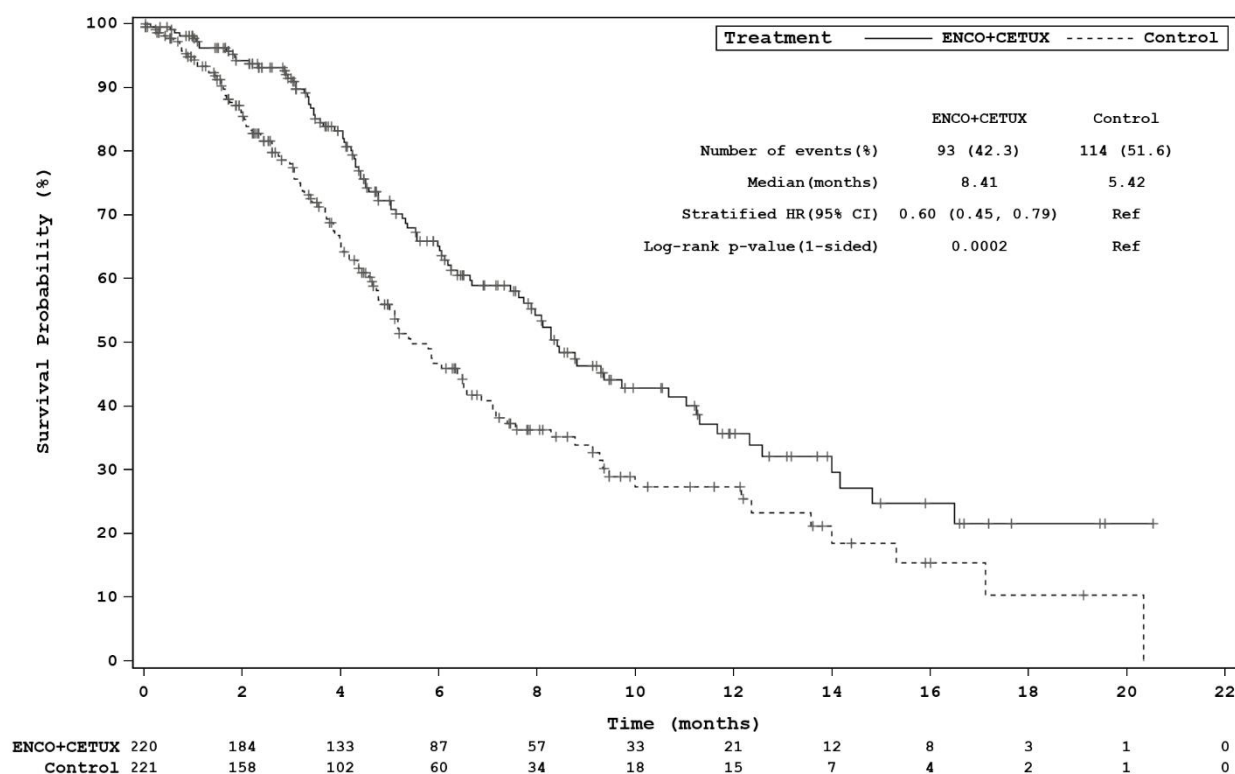
^e Among the first 331 randomised patients

^f Clopper-Pearson's method

^g Cochran Mantel-Haenszel test

^h Nominal p-value

Figure 3: Study ARRAY-818-302: Kaplan-Meier plot of Overall Survival (cut-off date: 11 February 2019)



BRAF V600E Mutant metastatic colorectal cancer – encorafenib in combination with cetuximab and FOLFOX - Study C4221015

Encorafenib in combination with cetuximab and mFOLFOX6 in first line treatment was evaluated in an open-label, multicenter, randomized phase 3 study (Study C4221015, BREAKWATER). Eligible patients were required to have MSS/pMMR (except if patients with dMMR or MSI-H status confirmed are unable to receive immune checkpoint inhibitor), RAS wildtype, BRAF V600E mutant metastatic colorectal cancer that was previously untreated. Prior use of BRAF inhibitors or EGFR inhibitors was prohibited. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status and region.

A total of 637 patients were randomised (1:1:1) to receive encorafenib 300 mg orally daily in combination with biweekly cetuximab dosed per its approved SmPC (n=158 – recruitment was discontinued during the study), or encorafenib 300 mg orally daily in combination with cetuximab and mFOLFOX6 (5-fluorouracil/folinic acid/oxaliplatin) dosed as per respective medicines approved SmPC (n=236) or Control (mFOLFOX6, FOLFOXIRI or CAPOX each with or without bevacizumab, n= 243). Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR) as assessed by a blinded independent central review committee (BIRC) comparing encorafenib 300 mg in combination with cetuximab and mFOLFOX6 versus Control. The key secondary endpoint was overall survival (OS). Efficacy results are summarised in Table 9 below.

The median age of patients treated with encorafenib 300 mg in combination with cetuximab and mFOLFOX6 was 61 years (range 24-84), 50 % were male and 59% were white. 54% of patients had baseline ECOG performance status of 0 and 48% of patients had at least 3 organs with tumour involvement at baseline.

The median duration of exposure was 11.5 months in patients treated with encorafenib 300 mg in combination with cetuximab and mFOLFOX6, and 6.0 months in patients treated with mFOLFOX6, FOLFOXIRI or CAPOX each with or without bevacizumab (Control arm). In patients treated with the combination of encorafenib 300 mg plus cetuximab and mFOLFOX6, the median relative dose intensity (RDI) was 90% for encorafenib, 93% for cetuximab, 80% for fluorouracil, 93% for folinic acid and 83% for oxaliplatin.

Encorafenib 300 mg in combination with cetuximab and mFOLFOX6 demonstrated a statistically significant improvement in PFS, ORR and OS, compared to Control. Efficacy results are summarised in Table 9 and Figure 4.

Table 9: Study C4221015: Efficacy Results

	Encorafenib with cetuximab and mFOLFOX6	mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab (Control)
Cut-off date: 22 December 2023 (ORR Primary analysis)		
ORR (per BIRC)		
Number of patients ^a	110	110
ORR n (%) (95% CI)	67 (60.9) (51.6, 69.5)	44 (40.0) (31.3, 49.3)
P-value ^{b,c,d}	0.0008	
Cut-off date: 06 January 2025 (PFS Primary analysis)		
PFS (per BIRC)		
Number of patients ^e	236	243
Number of events (%)	122 (51.7)	132 (54.3)
Median PFS, months (95% CI)	12.8 (11.2, 15.9)	7.1 (6.8, 8.5)
HR (95% CI) ^{c, f} P-value ^{d,g}	0.53 (0.41, 0.68) <0.0001	
OS		
Number of patients ^e	236	243
Number of events (%)	94 (39.8)	148 (60.9)
Median OS, months (95% CI)	30.3 (21.7, NE)	15.1 (13.7, 17.7)
HR (95% CI) ^{c, f} p-value ^{d,g}	0.49 (0.38, 0.63) <0.0001	
Median duration of follow-up, months (95% CI)	21.8 (20.4, 23.4)	22.2 (18.9, 23.5)

^a ORR Subset Full Analysis Set

^b p-value based on Cochran-Mantel-Haenszel (CMH) test

^c Stratified by ECOG PS by Randomization and Geographic Region by Randomization

^d 1-sided

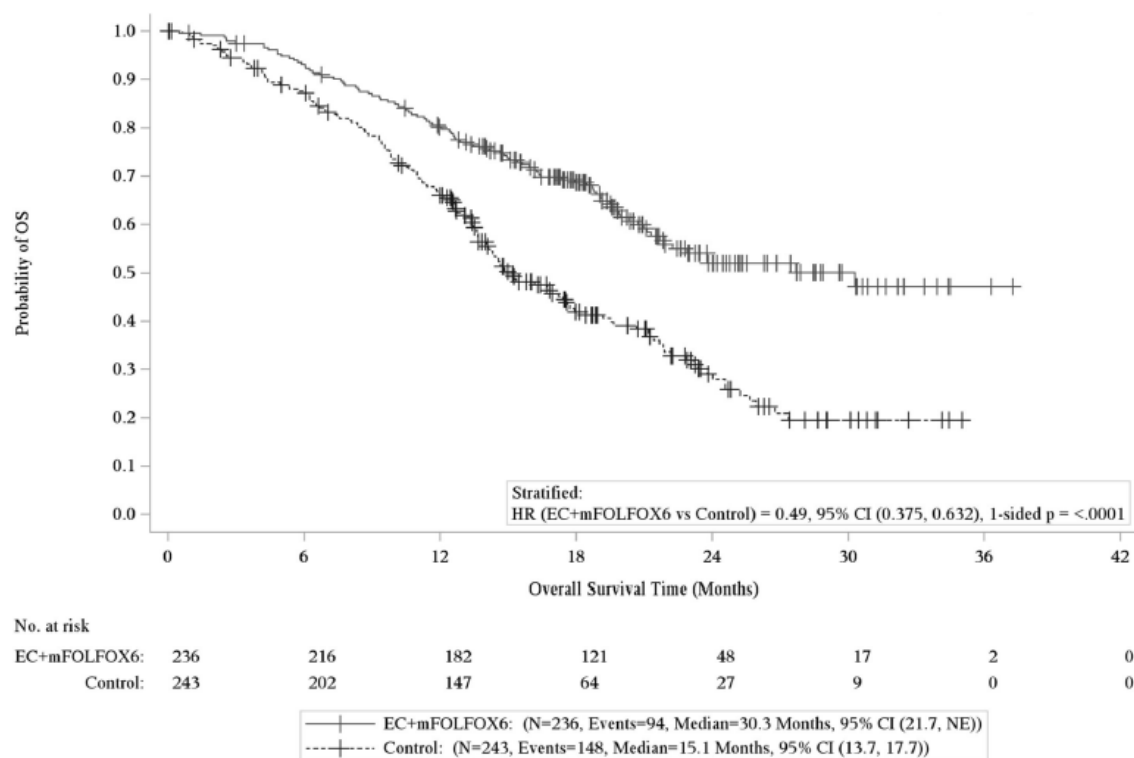
^e Randomised Phase 3, Full Analysis Set

^f Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favor of EC+mFOLFOX6 compared to Control

^g p-value from the log-rank test

BIRC = Blinded independent central review committee; CI = Confidence interval; HR = Hazard ratio; NE = Not Estimable; ORR = Objective response rate; OS = Overall survival; PFS = Progression free survival

Figure 4: Study C4221015: Kaplan-Meier plot of Overall Survival (cut-off date: 06 January 2025)



BRAF V600E Mutant advanced Non-small cell lung cancer – Study ARRAY-818-202

The safety and efficacy of encorafenib in combination with binimetinib were studied in a Phase II, open-label, multicentre, non-comparative study (Study ARRAY-818-202, PHAROS). Patients were required to have histologically-confirmed metastatic NSCLC with a BRAF V600E mutation, ECOG performance status of 0 or 1, and measurable disease. Patients had received 0 or 1 prior line of systemic therapy in the metastatic setting. Prior use of BRAF inhibitors or MEK inhibitors was prohibited.

Patients were enrolled based on the determination of a BRAF V600E mutation in tumour tissue or blood (e.g., ctDNA genetic testing) by a local laboratory assay. Central confirmation of the BRAF V600E mutation status (i.e. any short variant with protein effect V600E) was performed on archival or fresh tumour tissue collected at enrolment and utilized the FoundationOne CDx – F1CDx (tissue) assay.

The analytical sensitivity was assessed through the Limit of Detection (LoD) study for F1CDx using the hit rate method (defined as the lowest level with $\geq 95\%$ detection) by evaluating variant allele frequency (VAF) for short variants. For F1CDx, the median LoD for substitution was determined to be 3.2% VAF.

A total of 98 patients were enrolled and treated with encorafenib 450 mg orally once daily and binimetinib 45 mg orally twice daily. Treatment continued until disease progression or unacceptable toxicity.

The primary efficacy outcome measure was objective response rate (ORR) and was according to RECIST v1.1 as evaluated by an Independent Radiology Review (IRR). Secondary endpoints included duration of response (DoR), disease control rate (DCR), PFS and OS. Results of the primary analysis

with 18.2 months for treatment naïve and 12.8 months previously treated patients are presented below.

Of the 98 patients enrolled in this study, 59 (60.2%) patients were treatment naïve. The median age of patients was 70 years (47-86), 53% were female, 88% were white and 30% had never smoked. 74% had a baseline ECOG performance status of 1 (67.8 % of participants had a baseline PS 1 in the treatment naïve population and 82.1 % in the previously treated population). All patients had metastatic disease of which 8% had brain metastases at baseline and 97% had adenocarcinoma.

At the time of the primary analysis, the median duration of exposure was 15.1 months in treatment naïve patients and 5.4 months in previously treated patients. In the overall population, the median relative dose intensity (RDI) was 99.2% for encorafenib and 95.4% for binimetinib.

At the time of the primary analysis, the primary endpoint of IRR-assessed ORR in the treatment naïve population was 74.6% (95% CI: 61.6, 85.0), including 9 (15.3%) CRs and 35 (59.3%) PRs. The ORR by IRR in the previously treated population was 46.2% (95% CI: 30.1, 62.8), including 4 (10.3%) CRs and 14 (35.9%) PRs.

Results updated with an additional 10-month follow-up (median duration of exposure of 16.3 months in treatment naïve patients and 5.5 months in previously treated patients) are provided in Table 10.

Table 10: Study ARRAY-818-202: Efficacy Results

	Encorafenib with Binimetinib	
	Treatment Naïve (N=59)	Previously Treated (N=39)
ORR per IRR		
ORR, % (95% CI)	75% (62, 85)	46% (30, 63)
CR, %	15%	10%
PR, %	59%	36%
DoR per IRR	N=44	N=18
Median DoR, months (95% CI)	40.0 (23.1, NE)*	16.7 (7.4, NE)*
% with DoR ≥12 months	64%	44%

* Results from a sensitivity analysis considering new anti-cancer therapy as an event in addition to progression and death are 23.1 months in treatment naïve patients (14.8; NE) and 12.0 months (6.3; NE) in previously treated patients. N = number of patients; ORR = Objective Response Rate; CI = Confidence Interval; CR = Complete Response; PR = Partial Response; DoR = Duration of Response; IRR= Independent Radiology Review; NE = not estimable

Cardiac electrophysiology

In the safety analysis of pooled studies, the incidence of new QTcF prolongation >500 ms was 1.1% (4/363) in the Combo 450 ISP (n = 372), and 2.5% (5/203) in the encorafenib single agent group of patients with melanoma. QTcF prolongation of >60 ms compared to pre-treatment values was observed in 6.0% (22/364) patients in the Combo 450 ISP, and in 3.4% (7/204) in the encorafenib single agent group (see sections 4.2 and 4.4).

In the safety analysis of the Phase 3 (ARRAY-818-302) safety set in colorectal indication for patients who have received prior systemic therapy, the incidence of new QTcF prolongation >500 ms was 2.8% (6/216) and QTcF prolongation of >60 ms compared to pre-treatment values was observed in 8.8% (19/216) of patients of the encorafenib + cetuximab arm (see sections 4.2 and 4.4).

In the safety analysis of the pooled EC+FOLFOX population (Study C4221015, BREAKWATER) safety set in colorectal indication in first line treatment, the incidence of new QTcF prolongation

>500 ms was 4% (10/253) and QTcF prolongation of >60 ms compared to pre-treatment values was observed in 11% (29/253) of patients (see sections 4.2 and 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with encorafenib in all subsets of the paediatric population in colorectal carcinoma and lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumours. The pharmacokinetics of encorafenib have been shown to be approximately dose linear after single and multiples doses. After repeat once-daily dosing, steady-state conditions were reached within 15 days. The accumulation ratio of approximately 0.5 is likely due to auto-induction of CYP3A4. The inter-subject variability (CV%) of AUC ranged from 12.3% to 68.9%.

Absorption

After oral administration, encorafenib is rapidly absorbed with a median T_{max} of 1.5 to 2 hours. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, at least 86% of the encorafenib dose was absorbed. Administration of a single 100 mg dose of encorafenib with a high-fat, high-calorie meal decreased the C_{max} by 36%, while the AUC was unchanged. A drug interaction study in healthy subjects indicated the extent of encorafenib exposure was not altered in the presence of a gastric pH-altering agent (rabeprazole).

Distribution

Encorafenib is moderately (86.1%) bound to human plasma proteins *in vitro*. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, the mean (SD) blood-to-plasma concentration ratio is 0.58 (0.02) and the mean (CV%) apparent volume of distribution (V_z/F) of encorafenib is 226 L (32.7%).

Biotransformation

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, metabolism was found to be the major clearance pathway for encorafenib (approximately 88% of the recovered radioactive dose). The predominant biotransformation reaction of encorafenib was N-dealkylation. Other major metabolic pathways involved hydroxylation, carbamate hydrolysis, indirect glucuronidation and glucose conjugate formation.

Elimination

Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, radioactivity was eliminated equally in both the faeces and urine (mean of 47.2%). In urine, 1.8% of the radioactivity was excreted as encorafenib. The mean (CV%) apparent clearance (CL/F) of encorafenib was 27.9 L/h (9.15%). The median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h).

Medicinal product interactions

No drug drug interaction was evidenced between encorafenib and cetuximab, and between encorafenib and FOLFOX.

Effect of CYP enzymes on encorafenib

Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. *In vitro*, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively). The effect of co-administering a strong CYP3A4 inducer on encorafenib exposure has not been studied in a dedicated trial. Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily in melanoma patients with modafinil, a moderate CYP3A4 inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to encorafenib alone.

Effect of encorafenib on CYP substrates

In vitro experiments indicate encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, as well as a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily in melanoma patients with a single dose of CYP probe substrate cocktail reduced midazolam 2 mg (CYP3A4 substrate) AUC by 82% and C_{max} by 74 %. It decreased omeprazole 20 mg (CYP2C19 substrate) AUC by 17 % and did not change C_{max} and increased caffeine 50 mg (CYP1A2 substrate) AUC by 27 % and C_{max} by 13 %. It decreased the ratio of losartan metabolite E3174 to losartan (CYP2C9 substrate) concentrations in urine by 28% and did not change the ratio of dextromethorphan metabolite (dextrorphan) to dextromethorphan (CYP2D6 substrate) concentrations in urine. These results indicate strong induction of CYP3A4, mild inhibition of CYP1A2 and no impact on pharmacokinetics of CYP2C19 substrates. From the urinary data, the inhibitory potency on CYP2C9 and CYP2D6 cannot be finally concluded. No data are available for CYP2D6 poor metabolisers. A single dose of encorafenib 450 mg and binimetinib 45 mg reduced bupropion 75 mg (CYP2B6 substrate) AUC and C_{max} by $\leq 25\%$. Repeated administration of encorafenib 450 mg daily and binimetinib 45 mg twice daily reduced bupropion AUC and C_{max} by $\leq 26\%$ and increased the AUC of the active metabolite hydroxybupropion by 49% indicating mild induction. For co-administration with UGT1A1 substrates that undergo gut extraction, a minor to moderate interaction is expected. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. Additionally, no differences in exposure have been observed clinically when binimetinib is co-administered with encorafenib.

Effect of transporters on encorafenib

Encorafenib was found to be a substrate of the P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. The involvement of several uptake transporter families (OCT1, OATP1B1, OATP1B3 and OATPB1) was investigated *in vitro* using relevant transporter inhibitors. The data suggest that hepatic uptake transporters are not involved in encorafenib distribution into primary human hepatocytes.

Effect of encorafenib on transporters

Repeated administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a OATP1B1, OATP1B3 and BCRP substrate) increased rosuvastatin C_{max} by 2.7-fold and AUC by 1.6-fold indicating a mild inhibition of OATP1B1, OATP1B3 and/or BCRP transporters.

In vitro, encorafenib inhibited the hepatic transporter OCT1, but is unlikely to be an effective inhibitor clinically. Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 at clinical concentrations. In addition, encorafenib may inhibit P-gp in the gut at the expected clinical concentrations.

Special populations

Age

Based on a population pharmacokinetic analysis, age was found to be a significant covariate on encorafenib volume of distribution, but with high variability. Given the small magnitude of these

changes and high variability, these are unlikely to be clinically meaningful, and no dose adjustments are needed for elderly patients.

No clinical data are available in the paediatric population. The safety profile in the pediatric population is unknown. In adolescents with BRAF V600-mutant metastatic melanoma aged 12 to <18 years, population pharmacokinetic simulations show that the following doses and dose reductions for the management of adverse reactions result in plasma exposure similar to that achieved in adults:

- Weighing 40 kg and more: the adult dose 450 mg QD with the same dose reductions: 300 and 225 mg QD.
- Weighing between 30 and <40 kg: 300 mg QD, dose reduction to 225 mg QD and then 150 mg QD,
- Weighing less than 30 kg: 225 mg QD, dose reduction to 150 mg QD.

Children under 12 years should not be treated with encorafenib.

Gender

Based on a population pharmacokinetic analysis gender was not found to be a significant model covariate on clearance or volume of distribution. As a result, no major changes in encorafenib exposure are expected based upon gender.

Body weight

Based on a population pharmacokinetic analysis, body weight was found to be a significant model covariate on clearance and volume of distribution. However, given the small magnitude of change in clearance and the high variability in the predicted volume of distribution in the model, weight is unlikely to have a clinically relevant influence on the exposure of encorafenib in adults.

Race

There are no clinically relevant differences in encorafenib PK between Asians and non Asians. There are insufficient data to evaluate potential differences in the exposure of encorafenib in other races or ethnicity.

Hepatic impairment

Results from a dedicated clinical study indicate a 25% higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib exposure.

The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver, based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

Renal impairment

Encorafenib undergoes minimal renal elimination. No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of encorafenib.

In a population pharmacokinetic analysis, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m²) or moderate (eGFR 30 to 59 mL/min/1.73 m²) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m²). A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant. The pharmacokinetics of encorafenib have not been studied in patients with severe renal impairment.

5.3 Preclinical safety data

In the 4-week and 13-week rat toxicity studies, clinical signs, reduced body weight reduced epididymides and prostate weights and microscopic findings in testes, epididymides, stomach and skin were noted. Partial reversibility of these findings was noted after a 4-week recovery period. No

NOAEL could be established for the 4-week study. The NOAEL determined in the 13-week study was more than 10-times human therapeutic exposures.

In the 4-week and 13-week monkey toxicity study, isolated/sporadic episodes of emesis and diarrhoea as well as ophthalmic lesions were observed at slightly above human therapeutic exposures. Ophthalmic lesions were partially reversible and consisted of a separation or detachment in the retina between the outer rods and cones layer and retinal pigmented epithelium at the central macula at the fovea. This observation was similar to that described in humans as central serous-like chorioretinopathy or central serous retinopathy.

Encorafenib was not genotoxic.

Fertility studies were not conducted with encorafenib. In the 13-week rat toxicology studies, encorafenib treatment at 6 mg/kg/d (dose level more than 5 times the human exposure at the therapeutic dose) resulted in decreased testes and epididymis weights with tubular degeneration and oligospermia. In the 13-week study, partial reversibility was noted at the highest dose level (60 mg/kg/d).

The embryo-foetal development study in rats indicated that encorafenib induced foetal toxicity with lower foetal weights and delays in skeletal development.

The embryo-foetal development study in rabbits indicated that encorafenib induced foetal toxicity with lower foetal weights and transitory changes in skeletal development. Dilatation of the aortic arc was observed in some foetuses.

Encorafenib was phototoxic in an *in vitro* 3T3 Neutral Red Uptake Test. Encorafenib was not a sensitiser in the *in vivo* mouse sensitization assay. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Copovidone (E1208)
Poloxamer 188
Cellulose microcrystalline (E460i)
Succinic acid (E363)
Crospovidone (E1202)
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Capsule shell

Gelatin (E441)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

Printing ink

Shellac (E904)
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Braftovi 50 mg hard capsules

Each pack contains either 28x1 or 112x1 hard capsules in polyamide/aluminium/PVC/aluminium/PET/paper perforated unit dose blisters.

Not all pack sizes may be marketed.

Braftovi 75 mg hard capsules

Each pack contains either 42x1 or 168x1 hard capsules in polyamide/aluminium/PVC/aluminium/PET/paper perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

Braftovi 50 mg hard capsules

EU/1/18/1314/001 28x1 hard capsules

EU/1/18/1314/003 112x1 hard capsules

Braftovi 75 mg hard capsules

EU/1/18/1314/002 42x1 hard capsules

EU/1/18/1314/004 168x1 hard capsules

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018

Date of latest renewal: 23 June 2023

10. DATE OF REVISION OF THE TEXT

19/06/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.