21 May 2026
EMADOC-1700519818-2963465
Medicinal Products for Human Use (CHMP)

Assessment report

Braftovi

International non-proprietary name: encorafenib

Procedure No. EMA/VR/0000304994

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADME	Absorption/Distribution/Metabolism/Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
ATP	Adenosine Tri-Phosphate
AUC	Area Under the Concentration Time Curve
BA	Bioavailability
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
BRAF	Serine/Threonine-Protein Kinase B-Raf
CDER	Center for Drug Evaluation and Research
CDK	Cyclin Dependent Kinase
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL/F	Total Clearance
Cmax	Maximum Observed Plasma Concentration
cMET	MET Proto-Oncogene, Receptor Tyrosine Kinase
CNS	Central Nervous System
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
cuSCC	Cutaneous Squamous Cell Carcinoma
D	Day
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT(s)	Dose Limiting Toxicity(ies)

DMC Data Monitoring Committee

DOR Duration of Response

EAIR Exposure Adjusted Incidence Rate

ECHO Echocardiogram

ECOG Eastern Cooperative Oncology Group

ECOG PS Eastern Cooperative Oncology Group-Performance Status

eCRF Electronic Case Report Form

EMA European Medicines Agency

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

EOT End of Treatment

EQ-5D-5L EuroQoL-5D-5 Level

ERK Extracellular Signal-Regulated Kinase

ESMO European Society for Medical Oncology

EU European Union

EWOC Escalation With Overdose Control

FACIT Functional Assessment of Chronic Illness

FACT-C Functional Assessment of Cancer Therapy-Colorectal Cancer

FAS Full Analysis Set

FDA Food and Drug Administration

FGFR Fibroblast Growth Factor Receptor

GCP Good Clinical Practice

HR Hazard Ratio

IB Investigator's Brochure

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ITT Intent to Treat

IVRS Interactive Voice Response System

KM Kaplan-Meier

LDH Lactate Dehydrogenase

LME Linear Mixed-Effects

LVEF Left Ventricular Ejection Fraction

MAA Marketing Authorisation Application

Max Maximum

MEB	Medicines Evaluation Board
MEK	Mitogen-Activated Protein Kinase Kinase
Min	Minimum
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NE	Not Estimable
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
NS	Not Specified
ORR	Objective Response Rate
OS	Overall Survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PDL-1	Programmed Death (Receptor) Ligand 1
pERK	Phosphorylated Extracellular Signal-Regulated Kinase
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-Kinase
PK(s)	Pharmacokinetic(s)
PopPK	Population PK
PPE	Palmar Plantar Erythrodysaesthesia
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PSUR	Periodic Safety Update Report
QD	Once Daily
QoL	Quality of Life
RAF	Serine/Threonine-Protein Kinase
RAS	Rat Sarcoma Viral Oncogene Homologue
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose

RTOR	Real-time oncology review
SAE	Serious Adverse Event
SC	Steering Committee
SCE	Summary of Clinical Efficacy
SD	Standard Deviation
Tmax	Time to Maximum Observed Plasma Concentration
TTR	Time to Response
ULN	Upper Limit of Normal
US	United States (of America)
vs.	Versus
Vz/F	Volume of Distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pierre Fabre Medicament submitted to the European Medicines Agency on 13 October 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include, in combination with cetuximab and FOLFOX, the first line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation for BRAFTOVI, based on the interim results from the pivotal Study C4221015 (BREAKWATER). This is an open-label, multicenter, 3-arm, randomized Phase 3 study of encorafenib plus cetuximab (EC) alone or in combination with mFOLFOX6 versus standard of care chemotherapy in first-line participants with BRAF V600E-mutant mCRC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The version 3.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0049/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 23 July 2020. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Martin Mengel

Timetable	Actual dates
Submission date	13 October 2025

Timetable	Actual dates
Start of procedure:	1 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	21 December 2025
PRAC Rapporteur's preliminary assessment report circulated on:	6 January 2026
Joint Rapporteur's updated assessment report circulated on:	22 January 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	29 January 2026
MAH's responses submitted to the CHMP on:	17 March 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 April 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed therapeutic indication

The claimed therapeutic indication in this procedure is:

> "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".

Epidemiology

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a major cause of cancer-related mortality. According to GLOBOCAN 2020, approximately 1.9 million new CRC cases and 935,000 deaths occurred globally, representing 10 percent of all new cancer diagnoses and 9.4 percent of cancer deaths in that year (Sung H; 2021). In Europe, CRC remains among the most frequent cancers, with an estimated 520,000 new cases and 250,000 deaths in 2020, making it the second most commonly diagnosed cancer and the second leading cause of cancer-related mortality in the region (ECIS 2024).

Despite advances in prevention, screening and systemic therapies, metastatic colorectal cancer (mCRC) continues to be associated with a high disease burden, including substantial years of life lost and marked societal and economic impact due to disability-adjusted life years and productivity losses (Vuik FE; 2023).

Biologic features

Among the spectrum of BRAF alterations detected in metastatic colorectal cancer (mCRC), the BRAF V600E substitution is by far the most prevalent. This point mutation in exon 15 results in a valine-to-glutamic acid change at codon 600 and confers a marked increase in kinase activity, estimated at approximately 500–700-fold above physiologic signaling levels. BRAF V600E drives constitutive MAPK pathway activation through RAS-independent monomeric signaling and is therefore classified as a Class I BRAF mutation. This contrasts with Class II mutations, which require constitutive dimerization for signaling, and Class III mutations, which exhibit impaired kinase activity and depend on upstream RAS activation. The BRAF V600E mutation leads to sustained ERK pathway activation, promoting uncontrolled tumor cell proliferation and dissemination. Clinically, BRAF V600E-mutant mCRC exhibits a characteristic metastatic pattern with a higher frequency of peritoneal and distant lymph node involvement and comparatively fewer lung metastases than BRAF wild-type disease. This distribution may reduce the feasibility of potentially curative surgical interventions. The presence of a BRAF V600E mutation is consistently associated with poor prognosis, including significantly shorter overall survival compared with BRAF wild-type tumours. Approximately one quarter of BRAF V600E-mutant mCRC cases exhibit MSI-H/dMMR, which has implications for responsiveness to immune checkpoint inhibition (Piercey O, 2024).

Clinical presentation, diagnosis and stage/prognosis

Approximately one quarter of patients with colorectal cancer (CRC) present with metastatic disease at initial diagnosis, and close to 50% will develop metastases during the course of their illness (Cervantes A; 2022). These proportions are confirmed by recent population-based and registry evaluations indicating that de novo stage IV disease occurs in about 20–25 percent of CRC cases and that around half of all patients eventually progress to metastatic disease (Loroña N; 2025).

BRAF V600-mutant CRC represents a distinct molecular subtype characterized by right-sided primary tumors, specific metastatic patterns, frequent association with microsatellite instability and an overall poor prognosis. Multiple clinical series consistently demonstrate inferior OS and PFS for BRAF V600-mutant compared with BRAF wild-type disease, both in first-line and later-line settings (Takeda 2021). In a cohort of 255 patients with metastatic CRC with confirmed BRAF V600E mutation, median PFS was 6.0 months in the first line after triple therapy with bevacizumab, median OS was 12.9 months (Martinelli E; 2022), remarkably before the approval and recommendation of encorafenib+cetuximab in the relapsed/refractory setting. Subsequent studies and meta-analyses have confirmed the strong negative prognostic impact of the BRAF V600E mutation (PLOS meta-analysis 2013; BRAF-mt reviews 2019–2024).

Management

In 2022 ESMO guideline (Cervantes A; 2022) recommended first line systemic therapy for MSS/pMMR UICC stage IV unresectable colorectal cancer with a BRAF V600E mutation is either a chemotherapy doublet (mFOLFOX6: leucovorin-5-fluorouracil–oxaliplatin; CAPOX: capecitabine-oxaliplatin; FOLFIRI: leucovorin–5-fluorouracil–irinotecan) or triplet (for right sided tumours in fit patients, FOLFOXIRI : leucovorin-5-fluorouracil–oxaliplatin-irinotecan) with or without bevacizumab. Due to cumulative toxicities of especially oxaliplatin, treatment can be deescalated to maintenance therapy with f.e. 5-FU plus antibody) in non-progressive patients with at least four months of treatment. Of note, combination of anti-EGFR antibody (like cetuximab) with chemotherapy cannot be recommended in BRAF-mutant tumours (Cervantes A, 2022).

Current NCCN- and ESMO guidelines already reflect the results of the pivotal study discussed in this current submission including cetuximab and encorafenib + mFOLFOX6 as recommended approach for previously untreated patients (ESMO living guideline v1.3).

2.1.2. About the product

Encorafenib (Braftovi), an orally available small-molecule BRAF inhibitor, received its first EU marketing authorisation in 2018 (EMEA/H/C/004580/0000) in combination with the MEK inhibitor binimetinib (Mektovi) for the treatment of adult patients with unresectable or metastatic melanoma harbouring a BRAF V600 mutation, supported by the pivotal COLUMBUS study (Dummer et al., 2018).

In BRAF V600E-mutant metastatic colorectal cancer (mCRC), BRAF-inhibitor monotherapy, including encorafenib, was shown to be clinically inactive. Preclinical studies in CRC models demonstrated rapid EGFR-mediated feedback reactivation of the MAPK pathway, thereby sustaining tumour proliferation despite BRAF(V600E) inhibition (Corcoran et al., 2012; van Geel et al., 2017). Early clinical experience further confirmed the lack of antitumour activity of BRAF inhibition alone in mCRC (Kopetz et al., 2010). In parallel, limited efficacy and the emergence of resistance to cetuximab plus irinotecan in BRAF-mutant disease were reported (Loupakis et al., 2009) and subsequently corroborated in larger series.

Study ARRAY-818-302 (BEACON CRC, Kopetz et al., 2019) established the clinical utility of combining encorafenib with cetuximab in patients with previously treated BRAF V600E-mutant mCRC, forming the basis for the extension of indication in the EU in 2020. The incremental contribution of binimetinib to the triplet regimen was limited, with no clinically relevant advantage over the doublet combination.

Current indications in the EU include:

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.

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 (EMEA/H/C/xxxx/WS/2538).

Indication approved: 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. For biomarker-based patient selection, see section 4.2.

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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant received Scientific Advice on the development of encorafenib for the first line treatment of metastatic colorectal cancer from the CHMP on 23 July 2020. The Scientific Advice pertained to the following clinical aspects:

- Regarding an open-label, multicenter, randomized Phase 3 study of encorafenib plus cetuximab with or without chemotherapy compared to SOC therapy:
- The proposed patient population and eligibility criteria;
- The use of cetuximab in both experimental arms as a Q2W regimen;
- The choice of mFOLFOX6, FOLFIRI, FOLFOXIRI, or CAPOX, with the option to add bevacizumab as comparator;
- The design and conduct of a safety lead-in to assess the experimental combination, PK and optimal dose;
- The choice of primary endpoint (FPS by BICR; single-reader) and secondary endpoint (OS), and the proposed testing method to maintain T1E;
- The adequacy of the design, if positive, to serve as the single pivotal trial to support an extension application;
- The proposed stratification factors for randomisation;
- The proposed PK sampling scheme, PK analysis strategy, and exposure-response analysis plans for the Phase 3 portion
- The proposed PRO instruments, and their frequency and timing of administration

2.2. Non-clinical aspects

No new non-clinical data have been submitted as part of this application.

2.2.1. Ecotoxicity/environmental risk assessment

An updated ERA has been provided for Braftovi for the current procedure. The updated ERA is based on the ERA submitted for the initial marketing authorisation, which at that time was considered complete and acceptable.

No new experimental studies were provided for the present application. An updated $PEC_{surfacewater}$ value of 0.0557 µg/l was calculated for Braftovi, exceeding the action limit. The Applicant refined the Fpen values based on prevalence estimates for each included indication. Based on the submitted Phase II ERA PEC/PNEC calculations, a risk to the aquatic, sediment and groundwater and STP compartments is not indicated. Assessment of the terrestrial compartment was not considered necessary.

Table 1: Summary of main study results: Phase I

Substance (INN/Invented Name):	**Encorafenib**
CAS-number (if available):	1269440-17-6
PBT/vPvB screening	

Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD107	log Dow (pH 4) = 2.5 log Dow (pH 7) = 2.6 log Dow (pH 9) = 1.0	Potential PBT: N

PBT/vPvB assessment			
Property	**Parameter**	**Result**	**Conclusion**
Persistence	$DT_{50,\ sediment}$ at 20°C	1000 d/468.6	vP
PBT/vPvB statement:	Encorafenib is considered to be not PBT, nor vPvB		

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined (prevalence)	0.0557	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 2: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 301 / 352 l kg^{-1} (sludge) K_{OC} = 1,786 / 794 / 941 l kg^{-1}(soil)	No soil assessment required
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	**System 1** Parent: $DT_{50,\ water\ 20\ °C}$ = 44.4 d $DT_{50,\ sediment}$ = 1,000 $DT_{50,\ whole\ system\ 20\ °C}$ = 468.6 d NER = 15.2 % (test end) **System 2** Parent: $DT_{50,\ water\ 20\ °C}$ = 19.3 d $DT_{50,\ sediment}$ =1,000 d	Encorafenib is classified as very persistent

		$DT_{50,\ whole\ system\ 20\ °C}$ = 203.7 d NER = 17.7 % (test end)			
Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Pseudokirchneriella supcapitata	OECD 201	NOEC	750	µg/L	growth rate
Daphnia sp. Reproduction Test/ Daphnia magna	OECD 211	NOEC	210	µg/L	reproduction
Fish, ELS, Danio rerio	OECD 210	NOEC	10000	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000000	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/Chironomus riparius	OECD 218	NOEC	558	mg/kg_{dw}	development, normalised to 10% o.c.
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	0.0557 µg/L	100000 µg/L	5.6×10^{-7}		No risk
Surface water	0.0557 µg/L	21 µg/L	2.65×10^{-3}		No risk
Groundwater	0.0139 µg/L	2.1 µg/L	6.6×10^{-3}		No risk
Sediment	10.1 mg/kg_{dw}	5580 mg/kg_{dw}	1.8×10^{-3}		No risk

However, Braftovi has to be classified as very persistent (vP) in water/sediment systems as encorafenib showed a half-life (DT50) of 1000 days in sediment at 20 °C and DT50 of 203.7 - 468.6 days in the total system at 20 °C.

For PBT assessment a logDow value of 2.6 at pH 7 (2.5 at pH4, 1.0 at pH 9) was presented.

2.2.2. Discussion on non-clinical aspects

The lack of non-clinical pharmacology studies is acceptable, as Braftovi is already authorised for the second-line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation.

The new indication falls in scope of the ICH S9 guideline, therefore, the abbreviated non-clinical programme applied for the initial development is adequate.

Environmental risk assessment

An environmental risk assessment was performed for encorafenib in accordance with the current guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.). Since the log Dow/log Kow value is acceptable and below the threshold of 4.5, no further PBT assessment was required.

2.2.3. Conclusion on the non-clinical aspects

Environmental risk assessment

The environmental risk assessment for encorafenib indicated no risk to the aquatic, sediment, groundwater and STP compartments. Encorafenib is classified as very persistent (vP).

Appropriate disposal and handling precautions included in the SmPC are considered adequate to minimise potential environmental risks.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3 Overview of Encorafenib Clinical Studies in Cancer Patients

Study Code (see corresponding CSRs)	**Study Title**	**Number of Participants**	**Encorafenib Formulation[1]**	**PK Sampling[2]**
CLGX818X2101	A Phase I, multicentre, open-label, dose-escalation study of oral LGX818 in adult patients with locally advanced or metastatic BRAF mutant melanoma	72	Micro-emulsion-based solution and capsule	Rich
CMEK162X2110	A Phase Ib/II, multicentre, open-label, dose-escalation study of LGX818 in combination with MEK162 in adult patients with BRAF V600-dependent advanced solid tumours	126	Capsule	Rich
CLGX818X2109	The LOGIC 2 trial A Phase II, multi-centre, open-label	158 (Part 1)	Capsule	Sparse

Study Code (see corresponding CSRs)	Study Title	Number of Participants	Encorafenib Formulation[1]	PK Sampling[2]
	study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma			(Part 1)
CMEK162B2301 Part 1 and Part 2	COLUMBUS – Combined LGX818 used with MEK162 in BRAF mutant Unresectable Skin cancer: A 2-part Phase III randomised, open-label, multicentre study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma	921	Capsule	Sparse
CLGX818X2103	A Phase 1b/2 Multicentre, Open-Label, Dose-Escalation Study of LGX818 and Cetuximab or LGX818, BYL719, and Cetuximab in Patients with BRAF mutant Metastatic Colorectal Cancer	Whole study and PK dataset: 26 participants (Doublet, Phase Ib)	Capsule (encorafenib)	Rich (Phase 1)
		Phase 2: 50 (Doublet) PK dataset Phase 2: 28 participants (Doublet)	Capsule (encorafenib)	Rich and Sparse (Phase 2)
ARRAY-818-302 BEACON CRC	A Multicentre, Randomised, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusion of 5-Fluorouracil (5-FU)/Folinic Acid (FA)	CSLI: 37 participants (30 SLI, 7 JSLI) included in efficacy, PK and safety analyses Phase 3 Portion: 665	Capsule (encorafenib)	Rich in CSLI Phase and Sparse in Phase 3

Study Code (see corresponding CSRs)	Study Title	Number of Participants	Encorafenib Formulation[1]	PK Sampling[2]
	/Irinotecan (FOLFIRI)/Cetuximab with a Safety Lead-In of Encorafenib + Binimetinib + Cetuximab in Patients with BRAF ^{V600E}-mutant Metastatic Colorectal Cancer	participants (224 Triplet Arm, 220 Doublet Arm, 221 Control Arm) PK dataset: 230 participants (58 Triplet Arm, 73 Doublet Arm, 99 Control Arm)		
C4221015 BREAKWATER	An Open-Label, Multicentre, Randomised Phase 3 Study of First-Line Encorafenib Plus Cetuximab With or Without Chemotherapy Versus Standard of Care Therapy With a Safety Lead-In of Encorafenib and Cetuximab Plus Chemotherapy in Participants With Metastatic BRAF V600E Mutant Colorectal Cancer	SLI: 57 participants (EC + mFOLFOX6: 27 participants; EC + FOLFIRI: 30 participants) Phase 3 portion: 637 participants (EC: 158 participants; EC + mFOLFOX6: 236 participants ; Control arm : 243 participants)	Capsule (encorafenib)	Rich in SLI Phase and Sparse in Phase 3

[1] For detailed descriptions of clinical formulations and drug product, please refer to initial MAA Module 3.2.P.2.2; Pharmaceutical Development. [2] >6 samples per 24-hour period=Rich; ≤5 samples per 24-hour period=Sparse. Note: Study to support NSCLC indication (C4221008) is not included in this table. Abbreviations: BRAF=B-Raf proto-oncogene, serine/threonine-protein kinase; SLI=safety lead-in

2.3.2. Pharmacokinetics

Methods

Bioanalytical methods

Encorafenib and LHY746

Specific and sensitive bioanalytical methods using liquid chromatography with tandem mass spectrometry (LC-MS/MS) were developed and validated for the measurement of encorafenib and LHY746 in human plasma samples from the BREAKWATER study at PPD Middleton, WI, USA and at WuXi AppTec, Shanghai, China. To demonstrate the relationship between the 2 validated assay methods, a cross validation was performed (C4229004/ 400018-202815-PMV Cross Validation Report).
Analytical interference of encorafenib and LHY746 was tested with Quality Controls Fortified with Leucovorin, Irinotecan, Oxalipatin, 5-FU, and SN38, as well as concomitant medications (midazolam, omeprazole, bupropion, caffeine, modafinil and metabolites) for the PPD method.

Population pharmacokinetic modelling

A "global" population PK model was built including data from 1310 participants who received encorafenib, as monotherapy or in combination with binimetinib or other agents, from 9 Phase 1, 2, and 3 Studies. Included studies were: ARRAY-162-105, PHAROS/ARRAY- 818-202 (C4221008), LGX818X2103 (C4221001), MEK162B2301 COLUMBUS (C4221004), MEK162X2110 (C4221005) ARRAY-818-302 BEACON (C4221009), LGX818X2101 (C4221010), LGX818X2109 LOGIC 2 Part 1 (C4221013) and POLARIS 201 (C4221006). Overall, 716 (55%) participants were male, 1178 (90%) participants were white, the median (range) baseline age was 58 years old (19-94 years) and the median (range) baseline body weight was 76 kg (34-168 kg). In total, there were 8651 observations from 1299 participants evaluated in this population PK analysis, excluding 263 values that were BLQ (<3%). Eleven (11) participants were not included due to missing PK or only BLQ values.

Based on previous reports, a two-compartment model was used to characterize encorafenib PK. Several different forms of absorption models were evaluated, including first-order absorption with and without lag-time, various combined zero-order and first-order absorption models, and a transit compartment absorption model. Base model development began with the first 28 days of Studies C4221001 and C4221010 (N=143, Nobs=1486). The two-compartment model with first-order absorption without lag time was found to be the most appropriate model to describe the population PK of encorafenib. The model structure was parameterized in terms of CL/F, Vc/F, Vp/F, and Q/F. An encorafenib concentration dependent Emax function was successful to describe the time-varying auto-induction of encorafenib. None of the observations in this base model met the criteria (|CWRES| > 6) for outlier evaluation.

For the final base model, the remaining studies were added and then the entire time course of observations available from all studies were included. The SCM analysis was performed using the final base model to investigate whether there were any covariates that significantly influenced encorafenib PK. In the SCM analysis, all the potential covariates listed in Table 4 were tested in the model.

Table 4: Potential Covariates Evaluated in Global Model Population Pharmacokinetic Analysis

PK Parameter	Baseline Covariates
CL/F	Age, body weight, sex, total bilirubin, total protein, albumin, AST, ALT, LDH, ECOG performance status, tumor type, concomitant use of CYP3A inhibitor or inducer, renal impairment, and combination treatment (monotherapy versus combination with binimetinib versus other combinations)
Vc/F	Age, body weight, sex
ka	Age, body weight, sex

LDH=lactate dehydrogenase; ECOG=Eastern Cooperative Oncology Group; AST=aspartate aminotransferase; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; PK=pharmacokinetic; CL/F=apparent clearance; V_c=central volume of distribution; ka=absorption rate constant; 1L=treatment-naive; 2L=previously treated.

For categorical covariates, race was not evaluated since 90% of participants were white and thus this covariate assessment was not considered meaningful. Similarly, 99% of participants had either absence of use or concomitant administration of only a weak CYP3A inducer so concomitant CYP3A inducer category was not evaluated. Only 5% of participants received a strong CYP3A inhibitor so concomitant CYP3A inhibitor was evaluated as absence of use or concomitant administration of only weak CYP3A inhibitor versus use of concomitant moderate or strong CYP3A inhibitor. Furthermore, the only tumor types represented by at least 10% of the analysis population were melanoma and CRC. Therefore, tumor type was evaluated as melanoma versus CRC versus all other tumor types, which included healthy (1%), lung (7%), and Other (5%). Eastern Cooperative Oncology Group (ECOG) Performance status was evaluated as 0 versus 1 or greater, with missing values assigned to the most common value, ie, 0. Similarly, National Cancer Institute (NCI) was evaluated as 0 versus 1 or greater, with missing values combined with the most common value, ie, 0.

The full model was reached in 3 forward addition steps (α=0.05), which included the effect of age and tumor type on CL/F, as well as baseline body weight on Vc/F. Backward elimination was finalized after just 1 step as none of the 3 covariates selected during forward addition were eliminated during backwards elimination (a=0.001). All 3 relationships were found to be statistically significant upon removal (ie, removal resulted in greater than 10.83 increase in OFV) and thus all three covariate effects were retained in the final model. The final model resulting from the SCM analysis was subjected to a separate NONMEM run with $COV step executed. The SAEM IMP method was used in order to obtain standard error estimates. The IIV for parameters other than CL/F and Vc/F were fixed to a small number (15%), which is common practice when using the SAEM method. The IIV for ka was fixed to 50% since our ability to characterize the absorption phase was confounded. Three observations in the final model met the criteria for being considered outliers and were excluded. Equations for clearance and central volume of distribution without IIV are shown below. The final model parameters with confidence intervals are summarized in Table 5.

$$TVCL/F = 12.2L/h \cdot \left(\frac{AGE}{58}\right)^{-0.326} \cdot (1-0.175 \cdot mCRC) \cdot (1-0.0938 \cdot OtherTumor)$$

$$TVV2/F = 61.7L \cdot \left(\frac{BWT}{76}\right)^{0.588}$$

Table 5: Final model parameter estimates

Parameter	Estimate	RSE (%)	Shrinkage (%)	95% CI
$\theta_{\text{ka (h-1)}}$	0.954	3.342	-	(0.892 ; 1.017)
$\theta_{\text{CL/F Day 1}}(L/h)$	12.238	3.015	-	(11.515 ; 12.961)
$\theta_{\text{V2/F}}(L)$	61.730	2.583	-	(58.606 ; 64.855)
$\theta_{\text{Q/F}}(L/h)$	1.045	2.391	-	(0.996 ; 1.094)
$\theta_{\text{V3/F}}(L)$	54.549	2.376	-	(52.008 ; 57.090)
$\theta_{\text{Turnover HL}}(h)$	64.279	5.882	-	(56.869 ; 71.689)
θ_{EMAX}	1.861	2.534	-	(1.768 ; 1.953)
$\theta_{\text{EC50}}(ng/mL)$	9.097	4.016	-	(8.381 ; 9.813)
θ_{Gamma}	10.000	-	-	-
$\theta_{\text{Prop err}}$	0.589	1.026	-	(0.577 ; 0.601)
$\theta_{\text{mCRC tumor on CL/F Day 1}}(L/h)$	-0.175	26.883	-	(-0.267 ; -0.083)
$\theta_{\text{Other tumor type on CL/F Day 1}}(L/h)$	-0.094	55.241	-	(-0.195 ; 0.008)
$\theta_{\text{BWT on V/F Day 1}}(L)$	0.588	14.505	-	(0.421 ; 0.755)
$\theta_{\text{Age on CL/F Day 1}}(L/h)$	-0.326	20.740	-	(-0.459 ; -0.194)
IIV	CV (%)	RSE (%)	Shrinkage (%)	95% CI
IIV on $\theta_{\text{ka}}(\%)$	50	-	-	-
IIV on $\theta_{\text{CL/F}}(\%)$	56.48	4.183	12.985	(54.13 ; 58.74)
IIV on $\theta_{\text{V2/F}}(\%)$	50	5.650	30.445	(47.12 ; 52.73)
IIV on $\theta_{\text{Q/F}}(\%)$	15.81	-	-	-
IIV on $\theta_{\text{V3/F}}(\%)$	15.81	-	-	-
IIV on $\theta_{\text{HL}}(\%)$	15.81	-	-	-
IIV on $\theta_{\text{Emax}}(\%)$	15.81	-	-	-
IIV on $\theta_{\text{EC50}}(\%)$	15.81	-	-	-
IIV on $\theta_{\text{Gamma}}(\%)$	15.81	-	-	-
OFV	74720.610	-	-	-

Repository artifact ID FI-55846054. Line 1 substituted.
The 95% CIs were calculated based on standard errors from the NONMEM covariance step.
Table abbreviations: CI=confidence interval; CL/F=apparent initial clearance; V_2=central volume of distribution; Q/F=apparent inter-compartmental clearance; V_3=peripheral volume of distribution; CV=coefficient of variation; Prop=proportional; HL=half-life; EC50=concentration at half maximum effect; Emax=maximum auto-induction effect; IIV=inter-individual variability; OFV=objective function value; RSE=relative standard error.

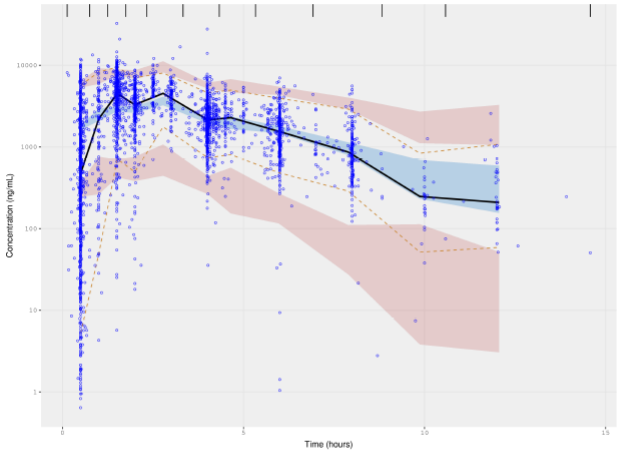
Encorafenib apparent clearance was estimated to be 12.2 L/h after the first dose in the typical adult participant and increased 186%, ie, up to 35 L/h, at steady-state as a result of autoinduction after multiple dosing.

The impact of the significant covariates is described as follows. Relative to the typical value of CL/F in melanoma participants, CL/F decreases 17.5 % in participants with mCRC and decreases approximately 9% in other participants (either healthy, lung tumors, or other solid tumors). Relative to the typical value of 12.2 L/h at the median age of 58 years, CL/F increases by 15% (to 14.0 L/h) at age 38 years and decreases by 7% (to 11.3 L/h) at age of 73 years. kg. Relative to the typical value of 61.7 L at the median body weight of 76 kg, V2/F decreases by 16% (to 51.6 L)

at baseline body weight of 56 kg and increases by 18% (to 72.5 L) at baseline body weight of 100 kg.

For model evaluation, visual predictive checks for concentration at day 1 (Figure 1) and day 14 (Figure 2) are depicted below.

Figure 1 Final Model VPC for Encorafenib Day 1



Repository artifact ID FI-55274195.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

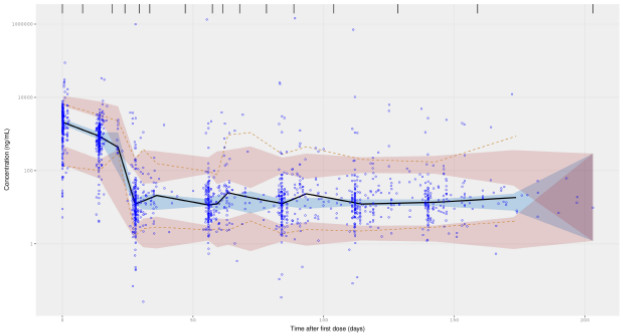
Figure 2 Final Model VPC for Encorafenib Day 14

Repository artifact ID FI-55274196.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

Subsequently, the global model was evaluated for adequacy in participants with BRAF V600-mutant mCRC in the BREAKWATER Study (Arm A, Arm B, and Cohort 2). PK parameters from previously developed global popPK model were used to evaluate the predictive performance of the model with the updated BREAKWATER Phase 3 data. No data fitting was done. Further, the observed PK data from the BREAKWATER study was compared to the 90% prediction interval of the simulated data, based on the final model parameters from the global model. The validation of the global population PK of encorafenib using data from BREAKWATER included 373 participants who received

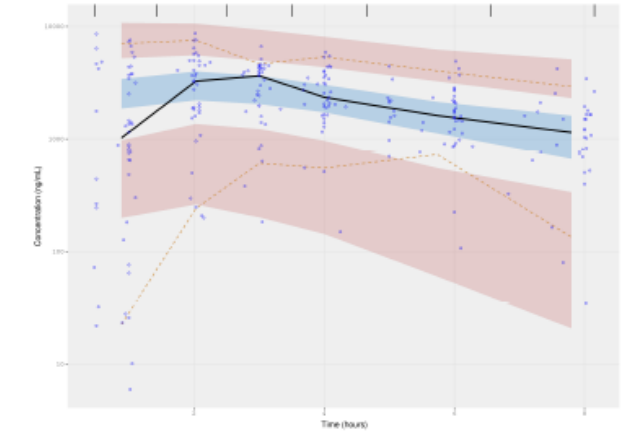
encorafenib in combination with cetuximab with or without chemotherapy, from Arm A, Arm B, and the safety lead-in (SLI) Cohort 2. Based on 1000 simulated trials using the parameter estimates from the final model (fixed and random effects), the 5th, 50th, and 95th percentiles for the observed data were mostly within the 95% CI for simulated data. The results are displayed in Figure 3 and Figure 4. The evaluation revealed that encorafenib PK data in participants with BRAF V600E-mutations were well described using a two-compartment model with first-order absorption and concentration-dependent auto-induction model. Based on the intrinsic or extrinsic factors evaluated in this analysis, no dose modifications are suggested.

Figure 3 VPC for Encorafenib For BREAKWATER Using Parameters from Final Global Model

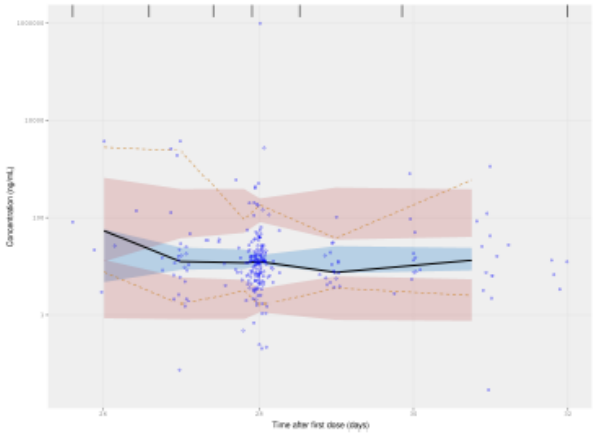


Repository artifact ID FI-56697547.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

Figure 4 Final Model VPC for Encorafenib For BREAKWATER on Day 1 (Upper Panel) and Day 28 (Lower Panel)



(a) FI-56697549



(b) FI-56697548

Repository artifact IDs are shown in subfigure labels.
Blue circles represent the observed data and the solid black line represents the 50th percentile of the observed data. The dashed red lines represent the 5th and 95th percentiles of the observed data. The blue ribbon represents the 95% CI of the 50th percentile of the simulated data. The red ribbons represent the 95% CI of the 5th and 95th percentiles of the simulated data.
Figure abbreviations: VPC=visual predictive check.

Pharmacokinetics in the target population

Pharmacokinetic (PK) data of encorafenib, as applied for in combination with cetuximab (EC) and mFOLFOX6 in patients with first-line mCRC with a BRAF V600E mutation, were obtained from the new pivotal Phase 3 study C4221015 (BREAKWATER). mFOLFOX6 is a Q2W chemotherapy regimen of combination Oxaliplatin 85 mg/m^2, Leucovorin 400 mg/m^2, and 5-FU (400 mg/m^2 IV bolus and 2400 mg/m^2 as IV infusion). Please see below efficacy section 10.2 for further study details.

Table 6 summarises details of the study and study interventions, e.g. PK sampling times relevant for the PK analyses, as discussed in the SCP (module 2.7.2) for the proposed treatment combination.

As support, a population PK (popPK) analysis was conducted and exposure-response (ER) of efficacy and safety were assessed through model-predicted exposure metrics and efficacy. Safety Lead In (SLI) and China mainland Phase 3 subgroup PK data were analysed using noncompartmental method; in addition, SLI and Phase 3 encorafenib PK data were included in the popPK modelling analysis.

The patients received daily 300 mg encorafenib as 4x75 mg capsules orally in the morning without regard to food. The combination treatment was administered as (bolus) infusions.

For the underlying application the following PK data sets were provided in module 2.7.2:

SLI PK Analysis Set: 27 in EC+mFOLFOX6 triplet Cohort, all with serial PK sampling and at least 1 PK parameter estimated for at least 1 of the analytes.

Phase 3 PK Analysis Set: 144 in EC Arm, 214 in EC + mFOLFOX6 Arm; all with sparse sampling, and 12 in EC Arm from mainland China with serial PK sampling and at least 1 encorafenib PK parameter estimated for at least 1 of the analytes. NCA-derived PK parameters from these 12 participants are reported in section 9.2.3

According to the Interim CSR (Phase 3 ORR PCD, Version 1.0, dated 22 May 2024), PK results in the SLI were obtained and reported for participants in the EC + mFOLFOX6 Cohort and in the EC + FOLFIRI Cohort for encorafenib, its inactive metabolite LHY746, and oxaliplatin and irinotecan and its metabolite SN-38, respectively. PK results in Phase 3 were obtained for participants in the EC Arm and the EC + mFOLFOX6 Arm for encorafenib and its metabolite LHY746.

In the SCP, the MAH indicated that PK sampling in the SLI portion was up to 8 hours so that the terminal plasma elimination half-life ($t_{½}$) and the AUC from time zero to infinity (AUC_{inf}) could not be reliably estimated, neither the accumulation ratio at steady state (AUC over the dosing interval [AUC_{tau}]/AUC_{inf}).

Table 6: Overview of study C4221015 PK data as relevant for the target indication

Study Name Study Description	Treatment Regimen (Formulation)	Primary Pharmacokinetic Objectives	Number of Participants in PK Analysis Set	PK Sampling	Data Cutoff Date	PK Analyses
BREAKWATER (C4221015) (Pivotal) Open-label, multicentre, 3-arm, randomised Phase 3 study of EC alone or in combination with mFOLFOX6 vs standard of care chemotherapy in first-line participants with $BRAF^{V600E}$-mutant mCRC. Prior to Phase 3, a 2-cohort SLI was conducted of EC in combination with standard of care chemotherapies in participants with $BRAF^{V600E}$-mutant mCRC who had ≤1 prior systemic regimen(s) for metastatic disease	**SLI** EC + mFOLFOX6 Cohort: encorafenib (capsule) 300 mg QD + cetuximab (IV) 500 mg/m^2 Q2W + mFOLFOX6 (IV) Q2W (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-FU 400 mg/m^2 [bolus] then 2400 mg/m^2)	**SLI** To characterise the PK of encorafenib, oxaliplatin and relevant metabolites To assess drug-drug interaction of encorafenib with oxaliplatin	**SLI** EC + mFOLFOX6 Cohort: 27	**SLI** Serial PK sampling for encorafenib, its metabolite (LHY746), and oxaliplatin (total platinum and platinum in plasma ultrafiltrate) at 1, 2, 3, 4, 6, and 8 hours postdose on C1D1 and C1D15 and predose on C1D1, C1D3, C1D15, C1D17, and C2D1 through C6D1	22 Dec 2023	NCA Population PK analysis Exposure-response analyses
	Phase 3 EC Arm (Arm A): encorafenib (capsule) 300 mg QD + cetuximab (IV) 500 mg/m^2 EC + mFOLFOX6 Arm (Arm B): encorafenib (capsule) 300 mg QD + cetuximab (IV) 500 mg/m^2 + mFOLFOX6 (IV) Q2W	**Phase 3** To evaluate trough concentrations of encorafenib and its metabolite LHY746 in Arm A and Arm B To characterise the PK of encorafenib and its metabolite LHY746 in participants randomised in mainland China (Arm A and Arm B)	**Phase 3** EC Arm: 144 EC + mFOLFOX6 Arm: 214	**Phase 3** Sparse PK sampling for encorafenib and its metabolite (LHY746) at predose on C1D1 through C6D1 in EC Arm (Arm A) and EC + mFOLFOX6 Arm (Arm B) For first 16 participants randomised in EC Arm (Arm A) in mainland China, serial PK sampling at 0.5, 1, 2, 3, 4, 6, 8, 24 hours postdose on C1D1 and C1D15 and predose on C1D1, C1D15, C2D1 through C6D1	06 Jan 2025 22 Dec 2023	Update of Population PK analysis Update of Exposure-response analyses

Note: Phase 3 China: in Table the 5 h sampling timepoint is missing

Results Safety Lead In part

Plasma PK parameters estimated using NCA methods for encorafenib and LHY746 for the triplet cohort, are summarised descriptively in Table 7. Encorafenib exposure was reduced on C1D15 compared to C1D1 and increased for LHY746 consistent with auto-induction by encorafenib. PK parameters for oxaliplatin (platinum in plasma and platinum in ultrafiltrate) are provided in DDI section 9.2.4.

Table 7: Descriptive summary of plasma PK parameters from SLI part study C4221015

Analyte	Parameter (Unit)		**Encorafenib + Cetuximab + mFOLFOX6** (N = 27)	
			Cycle 1 Day 1	Cycle 1 Day 15
Encorafenib	AUC0-6h (h•ng/mL)	n	21	14
		Geo mean (gCV (%))	9380 (97.4)	6130 (49.4)
	AUClast (h•ng/mL)	n	23	15
		Geo mean (gCV (%))	11500 (88)	7080 (36.7)
	CL/F (L/h)	n		15
		Geo mean (gCV (%))		32.7 (28.1)
	Cmax (ng/mL)	n	23	16
		Geo mean (gCV (%))	2870 (95.4)	2320 (59.8)
	Ctrough (ng/mL)			15
				11.9 (90.2)
	Tmax (h)	n	23	16
		Median (min-max)	2.77 (1.08-6)	2.16 (0.983-6)
LHY746	AUC0-6h (h•ng/mL)	n	21	14
		Geo mean (gCV (%))	1640 (109)	2820 (123)
	AUC_{last} (h•ng/mL)	n	23	15
		Geo mean (gCV (%))	2440 (90.7)	3770 (103)
	C_{max} (ng/mL)	n	23	16
		Geo mean (gCV (%))	582 (84.2)	873 (82.3)
	Ctrough (ng/mL)			15
				60.1 (304)
	T_{max} (h)	n	23	16
		Median (min-max)	7.28 (3-8.15)	3.98 (1-8)

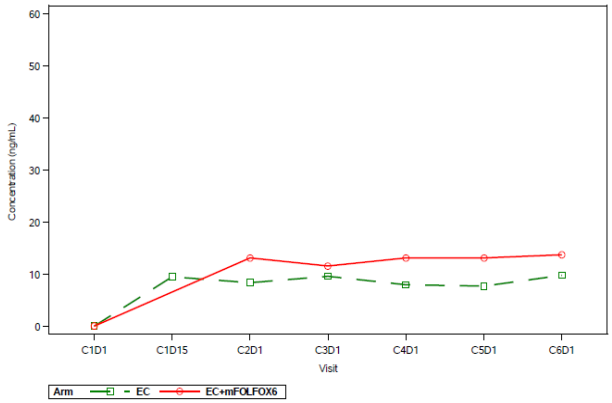
5Median trough concentrations of encorafenib and LHY746 were comparable between arms in combination with mFOLFOX6 or FOLFIRI.

6**Results Phase 3**

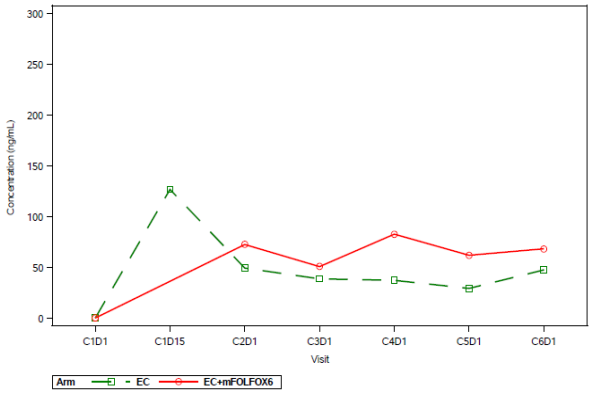
Steady-state C_{trough} levels were ~49 and 46% higher for encorafenib and LHY746, respectively, in combination with FOLFOX in the full phase 3 PK set. The MAH claimed that NCA conducted with data from the pivotal study would confirm the absence of an effect of oxaliplatin on encorafenib PK as exposures were consistent with historical data across studies, in the presence and absence of oxaliplatin.

Figure 5 Median trough Plasma Concentration - Time Plot (linear Scale) – Phase 3, PK

a) encorafenib



b) LHY746



Special populations

Race/Ethnicity

Systemic exposures from the first 12 mainland China participants from the encorafenib + cetuximab Arm (Arm A) are provided in Table 8.

Table 8: Descriptive summary of plasma PK parameters from Phase 3, China, study C4221015

Analyte	Parameter (Unit)		**Encorafenib + Cetuximab** (N = 12)	
			Cycle 1 Day 1	Cycle 1 Day 15
Encorafenib	AUC0-6h (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	15400 (61.2)	8010 (41.6)
	AUClast (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	26800 (47)	11100 (32.3)
	AUCtau (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	26800 (47)	11100 (32.2)
	CL/F (L/h)	n	9	11
		Geo mean (gCV (%))	11.4 (53.3)	27 (32.3)
	Cmax (ng/mL)	n	11	11
		Geo mean (gCV (%))	5200 (41.4)	3020 (55.7)
	Ctrough (ng/mL)	n		11
		Geo mean (gCV (%))		7.81 (85.8)
	Tmax (h)	n	11	11
		Median (min-max)	2 (1.02-24)	2 (0.533-24)
LHY746	AUC0-6h (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	2890 (63)	5100 (83.8)
	AUC_{last} (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	11900 (65.2)	11300 (103)
	AUCtau (h•ng/mL)	n	11	11
		Geo mean (gCV (%))	11900 (65.5)	11300 (103)
	CL/F (L/h)	n	11	11
		Geo mean (gCV (%))	871 (42.2)	1250 (76.7)
	Cmax (ng/mL)	n	11	11
		Geo mean (gCV (%))	871 (42.2)	1250 (76.7)
	Ctrough (ng/mL)	n		11
		Geo mean (gCV (%))		84.5 (343)
	T_{max} (h)	n	11	11
		Median (min-max)	6.07 (2-24)	3 (1.08-5.1)

Table 9 Descriptive statistics of encorafenib PK parameters [geometric mean (geometric CV%)] in Chinese and non-Chinese participants in CLGX818X2101, COLUMBUS and BREAKWATER studies

Study	Dose (mg)	Visit	C_{trough} (ng/mL)	C_{max} (ng/mL)	AUC_{0-6} (h.ng/mL)
CLGX818X2101 Encorafenib monotherapy	300 QD	C1D1	-	N=5 3310 (42.54)	-
		C1D15	N= 4 11 (135)	N=4 2920 (34.41)	-
		C2D1	N = 1 36 .8	-	-
		C3D1	N = 2 2 .88 (96.89)		-
COLUMBUS Encorafenib Arm CMEK162B2301 Part 1 + Part 2	300 QD	C1D15	N = 3 8.97 (15 .8)	-	-
		C1D16	N = 3 8.73 (24.3)	-	-
		C2D1	N = 105 7.55 (194.0)	-	-
		C3D1	N = 101 8.79 (234)	-	-
BREAKWATER Phase 3 non-Chinese patients encorafenib + cetuximab	300 QD	C2D1	N=86 10.44 (180)	-	-
		C3D1	N=83 10.60 (137)	-	-
BREAKWATER SLI non-Chinese patients encorafenib + cetuximab + mFOLFOX6	300 QD	C1D1	-	N=23 2870 (95.4)	N=21 9380 (97.4)
		C1D15	N=15 11.9 (90.2)	N=16 2320 (59.8)	N=14 6130 (49.4)
BREAKWATER Phase 3 non-Chinese patients encorafenib + cetuximab + mFOLFOX6	300 QD	C2D1	N=113 15.69 (229)	-	-
		C3D1	N=118 13.07 (179)	-	-
BREAKWATER Chinese patients encorafenib + cetuximab	300 QD	C1D1	-	N=11 5200 (41.4)	N=11 15400 (61.2)
		C1D15	N=11 7.81 (85.8)	N=11 3020 (55.7)	N=11 8010 (41.6)
		C2D1	N=16 6.303 (112)	-	-
		C3D1	N=19 12.31 (245)	-	-
BREAKWATER Phase 3 Chinese patients encorafenib + cetuximab + mFOLFOX6	300 QD	C2D1	N= 25 13.17 (172)	-	-
		C3D1	N= 20 13.92 (175)	-	-

C1D1: Cycle 1 Day 1; C1D15: Cycle 1 Day 15

Table 10 Encorafenib geometric mean (geometric CV%) Ctrough from Cycle 1 to Cycle 6 after repeated administration of encorafenib + cetuximab combination ± mFOLFOX6 in BREAKWATER study

Study	Dose (mg)	Visit	non-Chinese participants "row PK dataset" C_{trough} (ng/mL)	Chinese participants C_{trough} (ng/mL)	Ratio Chinese/non Chinese
SLI versus Chinese subgroup	300 QD	C1D15	N=15 11.9 (90.2)	N=12 7.737 (81)	0.650
Phase 3 Encorafenib + cetuximab	300 QD	C2D1	N=67 11.7 (190)	N=16 6.303 (112)	0.539
		C3D1	N=61 10.2 (114)	N=19 12.31 (245)	1.21
		C4D1	N=59 10.1 (188)	N= 18 8.766 (222)	0.868
		C5D1	N=59 8.25 (127)	N=13 23.25 (1316)	2.82
		C6D1	N=41 11.5 (187)	N=13 12.70 (121)	1.10
Phase 3 Encorafenib + cetuximab + mFOLFOX6	300 QD	C2D1	N=80 16.6 (253)	N= 25 13.17 (172)	0.793
		C3D1	N=87 13.0 (185)	N= 20 13.92 (175)	1.07
		C4D1	N=81 16.8 (179)	N= 24 19.81 (145)	1.18
		C5D1	N=69 17.0 (168)	N= 24 20.12 (314)	1.18
		C6D1	N=71 14.6 (120)	N= 18 16.24 (275)	1.11

Table 11 LHY746 geometric mean (± geometric standard deviation) Ctrough from Cycle 1 to Cycle 6 after repeated administration of encorafenib + cetuximab combination ± mFOLFOX6 in BREAKWATER study

Study	Dose (mg)	Visit	non-Chinese participants C_{trough} (ng/mL)	Chinese participants C_{trough} (ng/mL)	Ratio Chinese/non Chinese
SLI versus Chinese subgroup	300 QD	C1D15	N=15 60.1 (304)	N=11 84.5 (343)	1.42
Phase 3 Encorafenib + cetuximab	300 QD	C2D1	N=67 45.3 (276)	N=16 42.01 (160)	0.927
		C3D1	N=61 45.6 (191)	N=19 72.04 (127)	1.58
		C4D1	N=59 37.5 (222)	N= 18 61.03 (239)	1.63
		C5D1	N=59 31.0 (204)	N=13 84.55 (356)	2.73
		C6D1	N=41 52.9 (204)	N=13 82.32 (163)	1.56
Phase 3 Encorafenib + cetuximab + mFOLFOX6	300 QD	C2D1	N=80 58.2 (238)	N= 24 95.27 (103)	1.64
		C3D1	N=87 55.3 (240)	N= 20 90.31 (110)	1.63
		C4D1	N=81 68.9 (241)	N= 24 115.3 (90)	1.67
		C5D1	N=69 67.3 (204)	N= 24 75.44 (132)	1.12
		C6D1	N=71 64.7 (224)	N= 18 105.7 (156)	1.63

Pharmacokinetic interaction studies

No dedicated DDI studies were performed for this extension of indication application. SmPC section 5.2 stated from the previous EoI in combination with cetuximab that no DDI between encorafenib and cetuximab was observed.

In the EMA Scientific Advice from 2020, the DDI potential for the combinations of encorafenib and cetuximab in the safety lead-in part and its proposed evaluation were discussed. For patients in the EC + mFOLFOX6 cohort and in the EC + FOLFIRI cohort, the PK of encorafenib, its metabolite LHY746, and oxaliplatin and irinotecan and its metabolite SN-38, were analysed. The CHMP concluded that no DDIs were expected between encorafenib and cetuximab and between encorafenib and 5-FU or leucovorin, and agreed with the proposed approach.

The applicant further evaluated the potential for DDIs between encorafenib and irinotecan or oxaliplatin. Encorafenib has the potential to alter the PK of irinotecan and SN-38 and decrease their concentrations by approximately 25%, consistent with a CYP3A-mediated drug interaction. In the EC + mFOLFOX6, exposure to platinum in plasma and plasma ultrafiltrate, increased by 15% and 6%, respectively.

To further evaluate the potential effect of encorafenib on oxaliplatin plasma PK in the SLI portion of study C4221015, oxaliplatin PK was evaluated after multiple doses vs. after 1 dose of encorafenib. Oxaliplatin levels in plasma were measured as total platinum in plasma and total platinum in ultrafiltrate.

The geometric least squares mean ratios and 90% CIs of oxaliplatin plasma exposures evaluated as total platinum in plasma and ultrafiltrate on C1D15 to C1D1 were within 80-125% ranges (except upper limit of Cmax in ultrafiltrate), indicating absence of any significant impact of encorafenib on oxaliplatin PK.

2.4. Pharmacodynamics

No new pharmacodynamics data were submitted as part of this application.

2.5. PK/PD modelling

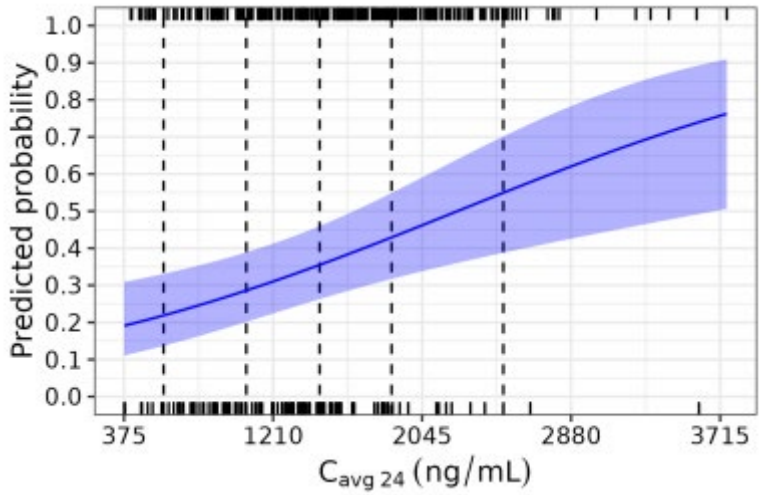
Exposure-response relationships for efficacy were performed in the target population for this application, that is, in patients with mCRC with a BRAF V600E mutation not previously treated from Arm B in Phase 3 portion of the study. There was no relationship identified between encorafenib exposure (derived using the popPK model) and the efficacy endpoint ORR (based on BICR). For PFS, encorafenib plasma exposure was neither found to have a significant ER relationship with PFS. The final model included an effect of baseline albumin on PFS, suggesting a higher baseline albumin is associated with a longer PFS which is consistent with previous publications that report that lower albumin is generally associated with poorer outcomes.

Both reports PMAR-EQDD-C422f-sNDA-1572 (ORR) and -3228 (PFS) concluded "Since all patients in this analysis received the same 300 mg QD dose of encorafenib, a relatively narrow range of encorafenib plasma exposures were included in this analysis, which may contribute to the lack of an identified E-R relationship for ORR/PFS in this analysis".

An exploration of the ER for selected safety endpoints in the pivotal study was conducted using data from 385 participants who had encorafenib plasma exposure metrics and who received EC or EC+mFOLFOX6 in the pivotal study (27 from SLI EC+mFOLFOX6 Cohort, 144 from Phase 3 EC Arm, and 214 from EC+mFOLFOX6 Arm). No statistically significant ER relationships were identified

between encorafenib exposure and the analysed all grades ADRs except for the encorafenib $C_{avg\ 24}$ and asthenia or any ≥ Grade 3 AE. The binominal logistic regression results indicated that participants with higher encorafenib $C_{avg\ 24}$ or who were female or who received concomitant chemotherapy (mFOLFOX6) were more likely to experience a Grade 3 or higher AE.

Figure 6 Simulations for Cavg 24 (ng/mL) and Any Grade 3 or Higher Adverse Event



2.5.1. Discussion on clinical pharmacology

PK data of encorafenib, as applied for in combination with cetuximab (EC) and mFOLFOX6 in patients with first-line mCRC with a BRAF V600E mutation, were obtained from the new pivotal Phase 3 study C4221015 (BREAKWATER).

The PPD bioanalytical method is validated and suitable for analysing encorafenib and LHY746 in study C4221015, including with cetuximab, FOLFOX/FOLFIRI components (leucovorin, irinotecan, oxaliplatin, 5-FU, SN38), and standard pre-medications. The WuXi method is also considered validated for these analytes; however, unlike PPD, it lacks interference validation for concomitant medications. Following method transfer to WuXi, substantial chromatographic changes were introduced, which may affect retention times and potential interference. Cross-validation was performed only using samples from a previous study (C4221006) without relevant co-medications, meaning interference from cetuximab, FOLFOX/FOLFIRI, or their pre-medications was not assessed. Therefore, signal suppression or enhancement cannot be excluded. The MAH's reliance on comparable PK results is not considered sufficient to replace proper bioanalytical validation. Full interference and cross-validation studies are required for future combinations. The oxaliplatin method is considered validated and suitable for study C4221015.
Standard methods and software have been used to develop the global model. It is agreed that the BREAKWATER data were overall in accordance with the previously investigated data.
The evaluation of trough plasma concentrations of encorafenib and the metabolite LHY746 in Arm A and Arm B and PK parameters of encorafenib and its metabolite LHY746 in participants randomized in mainland China (Arm A and Arm B, as appropriate) were only listed as exploratory endpoints of the pivotal study, in contrast to the investigation of potential impact of concurrent administration of chemotherapy on encorafenib and vice versa which were secondary endpoints.

Again, as for the SLI portion of the previous BEACON study to evaluate PK of encorafenib and cetuximab, the MAH used only a limited full sampling period until 8 hours post dose which resulted in unevaluated PK of the elimination phase and dependent PK parameters. The MAH did not adhere

to the Scientific Advice (EMA/CHMP/SAWP/372683/2020) to draw two additional samples thereafter for this purpose. In the previous BEACON study Safety Lead In, encorafenib geomean C_{max} (here: concentration at 2h) at C2D1 was 2490 ng/ml in the presence of cetuximab, and in the current SLI at C1D15 for the triplet 2320 ng/ml was measured for C_{max}.

The MAH claimed that the new NCA results would confirm the absence of an effect of oxaliplatin on encorafenib PK as exposures were consistent with historical data across studies, in the presence and absence of oxaliplatin. While this seemed justified from the SLI part for C_{max}, it could be noted that the trough levels at C2-C6D1 of the complete PK set in the triplet combination in phase III showed that encorafenib and LHY746 concentrations were somewhat higher (~49% and 46%) , respectively, than with E+C. The proposed statement in the SmPC 5.2 No drug-drug interaction was evidenced between encorafenib and cetuximab, and between encorafenib and FOLFOX is, however, agreed.

No cetuximab plasma sampling for PK was performed in this study in any of the cohorts. Considering that the proposed dosing is 500 mg/m² Q2W, in contrast to the 400 mg/m² /250mg/m² QW dosing in the approved EC combination, no information is available about cetuximab exposures in the proposed triplet with mFOLFOX6. This was already commented during the EMA Scientific advice that from the proposed dosing regimen no conclusions could be made whether the higher C_{max} and lower C_{min} would impact efficacy or safety. During approval of the EC combination, cetuximab C_{min} was measured with approximately 54.5 µg/ml which is comparable to approved levels in the cetuximab SmPC 5.2 for the weekly administration. Mean trough level from an approved biweekly regimen also is stated in that SmPC 5.2 with 31 µg/ml.

PK of encorafenib was also evaluated by popPK modelling. The BREAKWATER data were overall in accordance with the previously investigated data. No pharmacokinetic data are included in the popPK model for the metabolite LHY746, so that no conclusions can be drawn in this regard.

Special populations

PK data in Chinese patients are limited and insufficient for firm conclusions, with no full PK data for the triplet arm. While encorafenib exposure appears similar across ethnicities, the metabolite LHY746 shows consistently higher levels in Chinese patients. Due to data gaps and variability, no definitive conclusions on ethnic differences or dosing can be made.

With regard to other special populations, i.e. patients with renal and hepatic impairment, the MAH was asked to discuss the effects and relevance of the increase in the metabolite's exposure in these populations in Chinese patients. The MAH provided boxplots of metabolite exposure, however, all of these comparisons were impaired by the fact that for Chinese only encorafenib+cetuximab values were provided while all other subsets displayed the triplet exposure E+C+FOLFOX chemotherapy.

Drug interactions

The IC_{50} values for all the P450s studied were similar or higher for LHY746 than for encorafenib, with the exception of CYP2C8, suggesting that LHY746 may contribute to encorafenib's potential to cause drug-drug interactions from inhibition of CYP2C8.
In HLM, the IC_{50} of LHY746 was 8.3 µM for CYP2C9 and 9.5 µM for CYP2C8, whereas encorafenib inhibited 2C9 with ~5 µM and 2C8 with 20-30 µM (cf. module 2.5). In addition, inhibition of OAT3 by LHY746 had an IC_{50} of 9.4 µM in cells.

Specific details of the DDI evaluation of encorafenib and irinotecan an SN-38 has neither been presented nor discussed in module 2.7.2, although available in CSR ORR 5.3. This is considered acceptable as the indication treatment with EC + FOLFIRI is currently not sought. Therefore, these

data were not assessed. In case this indication would additionally be sought the DDI results should be submitted appropriately.

The geo-mean ratios and 90% CIs of oxaliplatin plasma exposures evaluated as total platinum in plasma and ultrafiltrate on C1D15 vs. C1D1 were within 80-125% ranges (except upper limit of C_{max} in ultrafiltrate), indicating absence of any significant impact of encorafenib on oxaliplatin PK.

Pharmacodynamics, biomarker

No additional data were presented for ER of encorafenib in the proposed triplet combination with mFOLFOX6, i.e. oxaliplatin, which is a known agent for QT prolongation. However, this issue has been addressed by additional information in SmPC 5.1, which is considered adequate from a PK point of view. 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.

The concordance of the BRAF V600E status between ctDNA and tumour tissue was 84%, of which 82.7% were both positive and 1.2% were both negative, 15.6% had BRAF V600E mutation positive only by central tumour testing and not via ctDNA testing. The concordance analysis is consistent with the higher sensitivity of tissue-based testing compared with liquid biopsy. ctDNA status decreased over time from baseline to C7D1 from detected to not-detected for all treatment arms (EC, EC+mFOLFOX6, control) and no specific advantage could be observed for the triplet over the other treatments. This was also comparable for the results over time for BRAF V600E %VAF.

With regard to the correlation between ORR (RECIST v1.1) and ctDNA clearance at Cycle 2 Day 15 (C2D15), only a limited association is observed. Specifically, ctDNA became undetectable in 11.6% and 7.0% of patients in the EC+mFOLFOX6 arm and the SOC arm, respectively, while the majority of patients with responses following imaging remained ctDNA-positive (62.8% and 69.0%, respectively). This limited concordance may be explained by the high analytical sensitivity of the assay used, with a clinical cut-off for positivity close to the limit of detection, which may not adequately capture relative changes in tumour burden.

Furthermore, C2D15 represents an early timepoint for the assessment of ctDNA clearance and may therefore not be optimal for evaluating treatment-related molecular response.

A treatment effect in favour of the EC+mFOLFOX6 arm is consistently observed across subgroups defined by ctDNA clearance status in both primary endpoints.

Acquired resistance was observed at higher frequencies without the addition of chemotherapy (37.9% vs. 6.6%).

The MAH informed that further genomic and transcriptomic analyses are ongoing and expected by end of Q1 2027. This is acknowledged (a post approval commitment REC will be submitted).

Exposure-response relationship

No relevant ER relationships were found for either efficacy or safety. This was anticipated in the CHMP Scientific Advice in 2020 concluding that "An exposure-response and exposure-safety analysis in the new indication is recommended, however, as only C_{trough} will be collected, and as only same dose encorafenib will be given to all patients, the exposure range will be narrow and the data to inform the exposure-response analysis will be limited". The only relevant positive ER relationship found was for $C_{ave,24}$ and asthenia and ≥grade 3 ADRs, but as said the underlying exposure range is very limited.

2.5.2. Conclusions on clinical pharmacology

The submitted clinical pharmacology dataset is limited from the pivotal study C4221015 with mainly sparse sampling. While for 300 mg encorafenib in the triplet combination with 500 mg/m² Q2W cetuximab and mFOLFOX6 no clinically significant differences in PK parameters were observed, in comparison to previous data. Considering no clinically relevant PK differences in the European target population, the clinical pharmacology data support this extension of the indication. The SmPC has been updated accordingly.

2.6. Clinical efficacy

2.6.1. Dose response study(ies)

The selection of the chosen dose is mainly based on the efficacy and safety results of the BEACON CRC trial in previously treated BRAF V600E Stage IV unresectable colorectal cancer, which led to the approval of encorafenib and cetuximab in the respective setting.

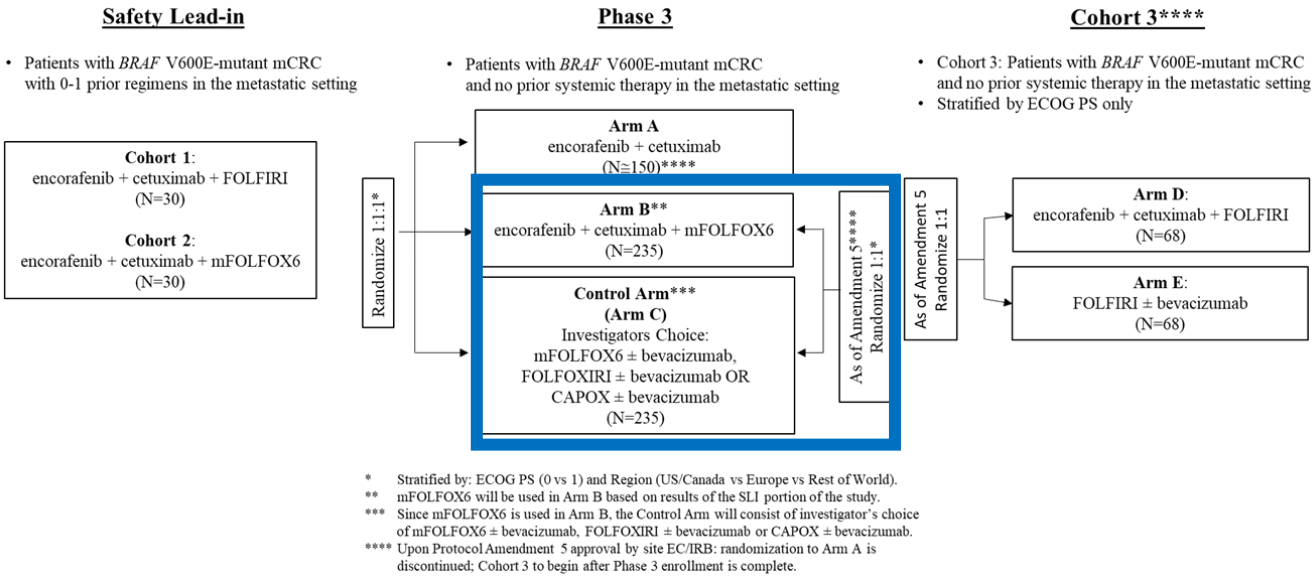
2.6.2. Main study(ies)

C4221015 (BREAKWATER)

Study C4221015 (BREAKWATER, NCT04607421; EudraCT 2020-001288-99) is an open-label, multiregional, randomized Phase 3 trial comparing encorafenib plus cetuximab with or without mFOLFOX6 to investigator's-choice standard oxaliplatin-based chemotherapy as first-line treatment for patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC). A two-cohort safety lead-in evaluated the tolerability and pharmacokinetics of encorafenib–cetuximab combined with either FOLFIRI or mFOLFOX6 before selection of mFOLFOX6 for the Phase 3 combination arm. In the Phase 3 portion, participants were initially randomized 1:1:1 to EC, EC+mFOLFOX6, or standard therapy, then 1:1 to EC+mFOLFOX6 or standard therapy after discontinuation of the EC arm. Treatment continued until centrally confirmed progression, unacceptable toxicity, withdrawal, or death, with subsequent survival follow-up. The dual primary endpoints are PFS and ORR by blinded independent central review.

The study design of the main study BREAKWATER (Study C4221015) is provided in Figure 7. In the remainder of the report, it is referred to the pivotal phase 3 part of the study and the final protocol after amendment 7 (31 May 2024) if not otherwise specified. The analyses presented in this report are based on a database snapshot date of 27 Jan 2025 and focus on the comparison between Arm B and the Control Arm.

Figure 7 Study Schema BREAKWATER (Study C4221015)as of Protocol Amendment 7 the phase III part used as pivotal evidence in the blue box



- **Methods**

Study participants

Key eligibility criteria

Male and female participants age ≥18 years (SLI) or ≥16 years (Phase 3 and Cohort 3) with BRAF V600E-mutant mCRC who met all inclusion criteria and did not meet any exclusion criteria were enrolled in this study.

Inclusion

- Participants with histologically or cytologically confirmed colorectal adenocarcinoma.
- Participants with evidence of Stage IV metastatic disease.
- Able to provide a sufficient amount of representative tumor specimen for central testing of BRAF V600E mutation status.
- Presence of a BRAF V600E mutation in tumor tissue or blood (eg, ctDNA genetic testing).
- Participants who had received ≤1 (SLI) or no (Phase 3 and Cohort 3) prior systemic regimen(s) for metastatic disease.
- ECOG performance status of 0 or 1.
- Measurable disease (Phase 3 and Cohort 3) and measurable or non-measurable but evaluable disease per RECIST, v1.1 (SLI), as assessed by Investigator and evidenced by available baseline scans.
- Adequate bone marrow, hepatic, and renal function.

Exclusion

- History of chronic inflammatory bowel disease that required medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to randomization.

- Presence of acute or chronic pancreatitis.
- Leptomeningeal disease.
- Impaired gastrointestinal function (eg, uncontrolled nausea, vomiting or diarrhea, malabsorption syndrome, small bowel resection) or disease which may have significantly altered the absorption of oral study intervention or recent changes in bowel function suggesting current or impending bowel obstruction.
- Clinically significant cardiovascular diseases.
- Colorectal adenocarcinoma that was RAS mutant or for which RAS mutation status was unknown
- Locally confirmed dMMR or MSI-H colorectal carcinoma or unknown MSI/MMR status. If participant had locally confirmed dMMR or MSI-H and was unable to receive immune checkpoint inhibitors due to a pre-existing medical condition, they were permitted to be enrolled.
- Concurrent or previous other malignancy within 2 years of study entry, except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease or prostate cancer with a Gleason score ≤6.
- Participants with active hepatitis B infection, active hepatitis C infection, evidence of active noninfectious pneumonitis, evidence of active and uncontrolled bacterial or viral infection within 2 weeks prior to start of study intervention, with certain noted exceptions for chronic infection with HIV, hepatitis B or hepatitis C.

Treatments

Table 12 Treatment Regimens in BREAKWATER, Phase 3 (Study C4221015)

Study Treatments	Dose	Frequency
Phase 3		
EC Arm (Arm A)		
Encorafenib	300 mg (4 × 75 mg) oral capsule	QD
Cetuximab	500 mg/m^2 (120-minute IV infusion)[a]	Q2W
EC + mFOLFOX6 Arm (Arm B)		
Encorafenib	300 mg (4 × 75 mg) oral capsule	QD
Cetuximab	500 mg/m^2 (120-minute IV infusion)[a]	Q2W
mFOLFOX6	Oxaliplatin 85 mg/m^2 (120-minute IV infusion)[a] Leucovorin 400 mg/m^2 (120-minute IV infusion)[a,b,e] 5-FU 400 mg/m^2 IV bolus, then 5-FU 2400 mg/m^2 continuous IV infusion over 46-48 hours[a]	Q2W
Control Arm (Arm C)		
mFOLFOX6 ± Bevacizumab	Oxaliplatin 85 mg/m^2 (120-minute IV infusion)[a] Leucovorin 400 mg/m^2 (120-minute IV infusion)[a,b,c] 5-FU 400 mg/m^2 IV bolus, then 5-FU 2400 mg/m^2 continuous IV infusion over 46-48 hours[a] Bevacizumab (optional; given per prescribing instructions)	Q2W 28-day Cycle
FOLFOXIRI ± Bevacizumab	Irinotecan 165 mg/m^2 (90-minute IV infusion)[a] Oxaliplatin 85 mg/m^2 (120-minute IV infusion)[a] Leucovorin 400 mg/m^2 (120-minute IV infusion)[a,b,c] 5-FU 2400 or 3200 mg/m^2 continuous IV infusion over 46-48 hours (per local standard of care)[a] Bevacizumab (optional; given per prescribing instructions)	Q2W 28-day Cycle
CAPOX ± Bevacizumab	Oxaliplatin 130 mg/m^2 (120-minute IV infusion)[a] Capecitabine 1000 mg/m^2 oral tablet Bevacizumab (optional; given per prescribing instructions)	Q3W 21-day Cycle BID Days 1-14

Note: The decision of which regimen to use in the Control Arm was at the participant/treating Investigator's discretion but must have been declared prior to randomization and the choice of regimen was not to be changed during the course of the participant's treatment. Note: Participants with colonic or rectal stent in place were not to receive bevacizumab in any of the Control Arm regimens. Note: In the Phase 3 portion of the study, participants were to receive their first dose of study intervention within 5 days of randomization.

Dose Modifications for encorafenib, cetuximab, and chemotherapeutic agents were allowed for toxicity management following guidance provided in the protocol. Encorafenib could be reduced to 225 mg QD or 150 mg QD in a second dose reduction. Cetuximab could be reduced to 400 mg/m² q2w or 300 mg/m² in a second dose reduction.

No dose reductions for bevacizumab were recommended. Administration of encorafenib as a single agent was not recommended.

Objectives and endpoints

The primary objective is to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus Arm C.

Table 13 Efficacy Objectives and Endpoints for Phase 3 of BREAKWATER Study

Objectives	Endpoints	Results in this SCE
Primary		
• To compare the efficacy of EC + mFOLFOX6 (Arm B) vs SOC (Control Arm [Arm C]) as measured by PFS and by ORR	• ORR by BICR	• ORR by BICR in the FAS, ORR Subset (N=220) as of ORR PCD (22 December 2023)
	• PFS by BICR, defined as the time from the date of randomization to the earliest documented disease progression per RECIST v1.1, or death due to any cause	• PFS analysis as of the PFS PCD (06 January 2025) in the FAS • Descriptive ORR by BICR analysis in the FAS as of the PFS PCD
Key Secondary		
• To further compare the efficacy of Arm B vs the Control Arm as measured by OS	• OS, defined as the time from the date of randomization to death due to any cause	• Analysis in the FAS as of the PFS PCD
Secondary (Descriptive Statistics Only)		
• To further evaluate the efficacy of Arm B vs the Control Arm as measured by ORR, DOR, PFS, PFS2, and TTR • To evaluate the efficacy of EC (Arm A) vs the Control Arm as measured by ORR, DOR, PFS, PFS2, TTR, and OS • To evaluate the efficacy of Arm A vs Arm B as measured by OS, PFS, PFS2, ORR, DOR, and TTR	• ORR by Investigator • ORR by BICR (Arm A vs Control Arm, Arm A vs Arm B) • DOR by BICR and by Investigator • PFS by BICR (Arm A vs Control Arm, Arm A vs Arm B) • OS (Arm A vs Control Arm, Arm A vs Arm B) • PFS by Investigator • TTR (by BICR and by Investigator), defined as the time from the date of randomization to first radiographic evidence of response (CR or PR) per RECIST v1.1 • PFS2, defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective PD by Investigator assessment, the second objective disease progression, or death from any cause, whichever occurs first	• ORR by Investigator, and DOR and TTR by BICR and by Investigator as of ORR PCD, ORR Subset (N=220) • ORR, DOR, and TTR analyses on the FAS as of the PFS PCD • PFS, PFS2 analyses on the FAS as of the PFS PCD • Efficacy data for Arm A not presented in this SCE

Predefined sensitivity/ supplementary analyses:

- PFS (BICR) in centrally Assessed BRAF V600E positive patients.

- Considering PD or death that occurs after the intercurrent events of starting new anticancer therapy as PFS events.

Sample size

Approximately 230 PFS by BICR events would be required to have at least 85% power to detect a hazard ratio of 0.67 between Arm B and Arm C using a 1-sided stratified log-rank test at a significance level of 0.023. The sample size of 235 participants per arm was determined based on the assumptions of a hazard ratio of 0.67 under the exponential model assumptions, and median PFS of 7 months on the Arm C.

The sample size of 220 participants (110 per arm) will provide 90% power for test of odds ratio of 2 proportions between the Arm B and Arm C using a 1-sided chi-square test at a significance level of 0.001 assuming an ORR by BICR of 35% and 65% for Arm C and Arm B, respectively.

Randomisation

Randomisation was stratified by ECOG (0 versus 1) and region (US/Canada versus Europe versus Rest of World).

Blinding

The study was designed as an open label study. Potential bias is addressed by central randomisation and BICR evaluation of imaging data.

Study assessments and procedures

Encorafenib was given daily, and cetuximab and FOLFOX were given every two weeks in the treatment arm and according to SmPC in the control arm. Tumour radiographic assessment was performed 42 to 49 days from the date of randomization then Q6W (± 7D) for the first 18 months after the date of randomization then Q8W (± 7D) thereafter or until BICR confirmed PD (regardless of new anticancer therapy), withdrawal of consent/assent, participant is lost to follow-up, death, or final OS analysis.

Statistical methods

Table 14 Relevant Analysis sets

Defined Analysis Set	Description
Enrolled	All participants who signed the Screening informed consent/assent document.
DLT-Evaluable Analysis Set	All participants who received at least 1 dose of study drug in the SLI and either experienced a DLT during the DLT evaluation period or completed this period without a DLT.
Full Analysis Set	Phase 3 and Cohort 3: all randomized participants, analysed according to treatment assigned at randomization.
Full Analysis Set, ORR Subset	First 110 participants randomized in each Arm B and Arm C for primary analysis of ORR/DOR/TTR.
Central BRAF V600E Positive Analysis Set	All randomized participants in Phase 3 and Cohort 3 with centrally confirmed BRAF V600E mutation.
Safety Analysis Set	All participants who received ≥1 dose of study drug.
PK Analysis Set	All treated participants with ≥1 analyte concentration result; participants analysed according to actual treatment received.
Biomarker Analysis Set	All participants in the Safety Set with ≥1 pre- or post-dose biomarker/pharmacodynamic assessment.

The primary estimands in the Phase 3 portion of the study were the treatment effect in progression-free survival (PFS) by blinded independent central review (BICR) and in ORR by BICR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) for Arm B vs Arm C. The hypothetical strategy was applied for the intercurrent events.

The primary objective in the Phase 3 portion of the study was to compare the efficacy, as measured by the primary endpoints of PFS by BICR and ORR by BICR, of Arm B versus Arm C. The following statistical hypotheses were tested to address the primary objective:

H_{01}: HR_{PFS} (B versus Control) ≥1 vs H_{11}: HR_{PFS} (B versus Control) <1

H_{02}: OR_{OR} (B versus Control) ≤1 versus H_{12}: OR_{OR} (B versus Control) >1

where HR_{PFS} (B versus Control) is the HR for PFS of Arm B versus the Control Arm and OR_{OR} (B versus Control) is the odds ratio for objective response of Arm B versus the Control Arm.

The key secondary objective is to compare the efficacy, as measured by the key secondary endpoint of OS, of Arm B versus Arm C. The following statistical hypothesis was tested to address the key secondary objective:

H_{03}: HR_{OS} (B versus Control) ≥1 vs H13: HR_{OS} (B versus Control) <1

where HR_{OS} (B versus Control) is the HR for OS of Arm B versus the Control Arm.

The following multiple testing strategy was specified in the SAP:

Eight months after randomization of the first 110 participants each in Arm B and in Arm C, or after the completion of enrolment of the Phase 3 portion of the study, whichever occurs later, the ORR by BICR will be compared for Arm B versus Arm C, on these first 220 participants, using a 1-sided alpha of 0.001.

If the results of ORR by BICR analysis are statistically significant, an interim analysis for OS on all participants will be conducted at this time using a portion of nominal 1-sided alpha of 0.001.

Once at least 230 PFS events by BICR will be observed for Arm B + Arm C and at least 12 months after the completion of enrolment of the Phase 3 portion of the study, the PFS analysis for the comparison of Arm B versus Arm C will be tested using a 1-sided alpha of 0.023.

If the results of PFS by BICR analysis are statistically significant, an interim analysis for efficacy OS will be conducted at this time using a portion of nominal 1-sided alpha of 0.023. The boundaries for the efficacy analysis will be derived using a Lan-DeMets alpha-spendingfunction1 that approximates O'Brien-Fleming stopping boundaries for overall type I error rate at 0.023 level (1-sided).

The primary efficacy analysis compared PFS time by BICR between Arm B and Arm C using a 1-sided stratified log-rank test (stratified by randomisation strata). The censoring and event date options to be considered for the PFS primary analysis are presented in the following table.

Table 15 PFS Outcome and event date – Primary Analysis

Situation	Date of Progression/Censoring	Outcome
No adequate baseline assessment, including no disease at baseline	Date of randomization[a]	Censored[a]
PD or death ≤12 (or 16)[b] weeks after last adequate tumor assessment or ≤12 weeks after date of randomization	Date of PD or death	Event
PD or death >12 (or 16)[b] weeks after the last adequate tumor assessment[c]	Date of last adequate tumor assessment[c] documenting no PD prior to new anticancer therapy, or missed assessments	Censored
No PD		
New anticancer therapy given[d]		

a If the participant dies ≤12 weeks after date of randomization, the death is an event with date on death date.

b Durations are equal to 2 times the length of the tumor assessment interval, which is 12 weeks for the first 18 months after randomization, and 16 weeks thereafter.

c If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of randomization; if the criteria is met, the censoring will be on the date of randomization.

d New anticancer therapy includes systemic therapy, radiation and surgery

The treatment effect was estimated using a Cox's proportional hazards model stratified by randomization strata to calculate the HR for PFS of Arm B versus Arm C, along with the corresponding 2-sided 95% CI and 2-sided 95.4% CI. Kaplan-Meier estimates (product-limit estimates) are presented by treatment arm together with a summary of associated statistics including the median PFS time with 2-sided 95% CI. The PFS at 3, 6, 9, 12, 15, 18 and 21 months was estimated with corresponding 2-sided 95% CIs.

Sensitivity analyses were performed to explore the robustness of the primary analysis results and the supportive estimands: A stratified analysis was performed to compare the PFS time by derived investigator assessment; an unstratified analysis was performed to compare the PFS time by BICR; PFS by BICR was analyzed based on Central BRAF V600E Positive analysis set; PFS by BICR was also analyzed based on RMST differences; multivariable Cox regression analysis were performed to explore the potential influences of baseline participant or disease characteristics on PFS; PFS by BICR was analyzed using the same methodology and summary as the main analysis, but including observations/events that occurred after >12 (or 16) weeks from last adequate post-baseline tumor assessment/start date.

As supplementary analysis, PFS by BICR was analyzed using the treatment policy strategy. The analysis used the same methodology and summary as the main analysis but included observations that occurred after the intercurrent events of starting new anticancer therapy.

For analysis of OR, the treatment effect of the Arm B compared to Arm C, as measured by stratified (by the randomization strata) odds ratio and its 95% CI and its 99.8% CI in terms of OR defined as the odds of OR with Arm B divided by the odds of OR with Arm C was tested using Cochran-Mantel-Haenszel statistics stratified by the randomization strata.

The key secondary efficacy analysis compared OS time between Arm B and Arm C using a 1-sided stratified log-rank test. The treatment effect was estimated using a Cox's proportional hazards model stratified by randomization strata to calculate the HR for OS of Arm B versus Arm C. In order to account for the group sequential design on this endpoint, the repeated CI method was used to construct the 2-sided repeated CI for the HR at the interim and the final analyses of OS, in addition to the unadjusted 2-sided 95% CI.

- **Results**

Participant flow

Figure 7 Participant Disposition (FAS, Phase 3 DCO 06 Jan 2025)

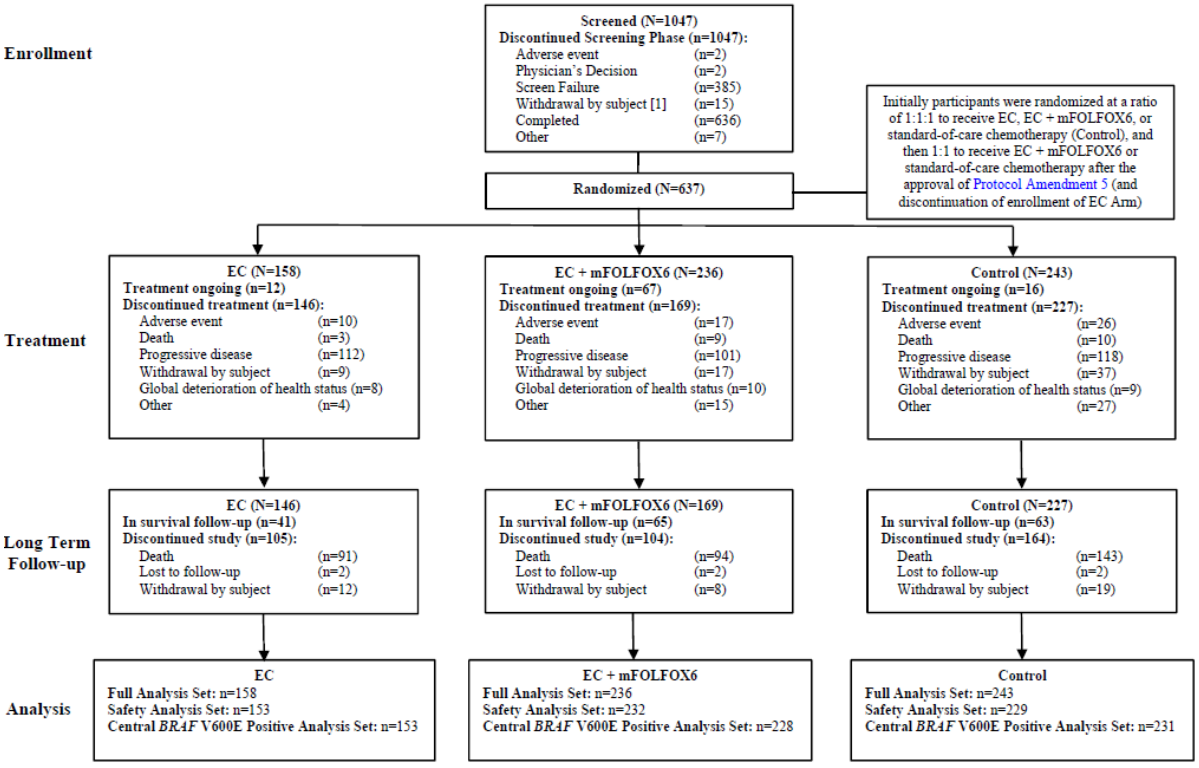


Table 16. Disposition Events Summary - Phase 3 Full Analysis Set (Protocol C4221015)

Number (%) of Participants	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Disposition phase: treatment			
Participants Entered:	158 (100.0)	236 (100.0)	243 (100.0)
Discontinued	146 (92.4)	169 (71.6)	227 (93.4)
Reason for discontinuation			
Adverse event	10 (6.3)	17 (7.2)	26 (10.7)
Death	3 (1.9)	9 (3.8)	10 (4.1)
Progressive disease	112 (70.9)	101 (42.8)	118 (48.6)
Withdrawal by subject	9 (5.7)	17 (7.2)	37 (15.2)
Global deterioration of health status	8 (5.1)	10 (4.2)	9 (3.7)
Other	4 (2.5)	15 (6.4)	27 (11.1)
Ongoing	12 (7.6)	67 (28.4)	16 (6.6)
Disposition phase: long-term follow-up			
Participants Entered:	146 (92.4)	169 (71.6)	227 (93.4)
Discontinued	105 (66.5)	104 (44.1)	164 (67.5)
Reason for discontinuation			
Death	91 (57.6)	94 (39.8)	143 (58.8)
Lost to follow-Up	2 (1.3)	2 (0.8)	2 (0.8)
Withdrawal by subject	12 (7.6)	8 (3.4)	19 (7.8)
Ongoing	41 (25.9)	65 (27.5)	63 (25.9)

Data cutoff date: 06JAN2025

Recruitment

Conduct of the study

The study was conducted between 21 December 2020 (FPFV) and 06 January 2025.

Randomization into the Phase 3 portion of the study was conducted between 16 November 2021 and 22 December 2023.

Analyses timing for the respective data cut-off is presented below.

Table 17 Hierarchical Testing Summary for Efficacy Endpoint

Primary/ Secondary	Endpoint	Data cutoff	Population	Criterion for Significance (p value[a])	Actual p value[a]
Primary	cORR by BICR	22 Dec 23	FAS, ORR Subset	0.001	0.0008
Primary	PFS by BICR	06 Jan 25	FAS	0.023	<0.0001
Key Secondary	OS	06 Jan 25	FAS	0.012[b]	<0.0001

[a] All p-values provided here are one sided
[b] According to the Lan-DeMets (O'Brien-Fleming) boundary corresponding to the information fraction available at the data cutoff (OS events).

Study amendments

Table 18 Summary of Main Protocol Amendments study C4221015 (BREAKWATER)

Amendment Version Date	Main important changes
Amendment 1 07 August 2020	- Early administrative and clarificatory updates to the original protocol (no major changes to overall study design reported in available excerpts).
Amendment 2 12 November 2020	- Added specific guidance on management of cancer patients during the COVID-19 pandemic, including risk assessment and mitigation..
Amendment 3 24 February 2021	- Further updates to the risk–benefit assessment and safety sections, including refinement of risk tables and mitigation strategies.
Amendment 4 28 February 2022	- Updated male and female reproductive inclusion criteria and contraceptive guidance, including extension of contraception duration for women of childbearing potential.
Amendment 5 20 December 2022	-**Discontinuation of enrollment in Arm A as likelihood to demonstrate superiority for EC vs SOC is low** - Added Cohort 3 (Arms D and E) to evaluate EC+FOLFIRI vs FOLFIRI ± bevacizumab in first-line patients, based on maturing SLI data showing tolerable safety and encouraging antitumour activity. - **Introduced ORR (Arm B vs Control) as an additional primary endpoint and updated objectives/estimands** (including OS as secondary endpoint and objectives/endpoints for Cohort 3). - Increased planned Phase 3 sample size and updated design text (overall design, intervention groups, duration).
Amendment 6 13 March 2024	- **Modified the required number of PFS events by BICR and corresponding power assumptions for the Phase 3 primary PFS analysis to enable a timely read-out given slower-than-expected event accrua**l. - Updated statistical testing strategy and minimal follow-up requirements; added condition that PFS in Cohort 3 will be analysed descriptively if ORR is not statistically significant. - Updated several safety, PK and operational sections (eg, ctDNA objectives/endpoints, photosensitivity wording, ECG and PK sampling, contraception text) in line with accumulated data and product information.
Amendment 7 31 May 2024	- Corrected randomisation ratio in Cohort 3 from planned 2:1 to the actually implemented 1:1 (Arm D: Arm E), with corresponding adjustments to Cohort 3 sample size and overall study sample size. - Refined power and required PFS events for Cohort 3 analyses following the randomisation change.

Protocol deviations

Table 19 Summary of Important Protocol Deviations – Phase 3 Full Analysis Set (Protocol C4221015)

Protocol Deviation Category	**EC (N=158) n (%)**	**EC+mFOLFOX6 (N=236) n (%)**	**Control (N=243) n (%)**
Number of participants with at least one important protocol deviation	48 (30.4)	89 (37.7)	77 (31.7)
Concomitant Medications	6 (3.8)	14 (5.9)	2 (0.8)
Inclusion/Exclusion	4 (2.5)	13 (5.5)	9 (3.7)
Informed Consent	7 (4.4)	6 (2.5)	11 (4.5)
Investigational Product	5 (3.2)	24 (10.2)	18 (7.4)
Procedures/Tests	23 (14.6)	27 (11.4)	37 (15.2)
Protocol Specific Discontinuation Criteria	2 (1.3)	2 (0.8)	1 (0.4)
Randomization	0	3 (1.3)	1 (0.4)
Safety Reporting	11 (7.0)	19 (8.1)	19 (7.8)

A participant with multiple deviations is counted in the corresponding categories.

Baseline data

Table 20. Demographic Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

	EC (N=158)	EC+mFOLFOX6 (N=236)	Control (N=243)	Total (N=637)
Age (Years), n (%)				
< 18	0	0	0	0
18 - < 65	105 (66.5)	150 (63.6)	139 (57.2)	394 (61.9)
>= 65	53 (33.5)	86 (36.4)	104 (42.8)	243 (38.1)
>=75	14 (8.9)	16 (6.8)	24 (9.9)	54 (8.5)
Median (range)	59.00 (26, 84)	60.00 (24, 81)	62.00 (28, 84)	61.00 (24, 84)
Mean (SD)	57.79 (13.21)	57.95 (12.71)	59.38 (12.89)	58.46 (12.90)
Sex, n (%)				
Male	79 (50.0)	123 (52.1)	119 (49.0)	321 (50.4)
Female	79 (50.0)	113 (47.9)	124 (51.0)	316 (49.6)
Race, n (%)				
Black or African American	1 (0.6)	0	1 (0.4)	2 (0.3)
American Indian or Alaska Native	1 (0.6)	0	0	1 (0.2)
Asian	64 (40.5)	88 (37.3)	91 (37.4)	243 (38.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	88 (55.7)	141 (59.7)	144 (59.3)	373 (58.6)
Other	0	0	0	0
Not reported	4 (2.5)	7 (3.0)	5 (2.1)	16 (2.5)
Multiracial	0	0	2 (0.8)	2 (0.3)
Ethnicity, n (%)				
Hispanic or Latino	16 (10.1)	28 (11.9)	30 (12.3)	74 (11.6)
Not Hispanic or Latino	131 (82.9)	187 (79.2)	201 (82.7)	519 (81.5)
Not reported	11 (7.0)	21 (8.9)	12 (4.9)	44 (6.9)
Racial Designation, n (%)				
Japanese	19 (12.0)	25 (10.6)	26 (10.7)	70 (11.0)
Korean	5 (3.2)	12 (5.1)	10 (4.1)	27 (4.2)
Chinese	38 (24.1)	48 (20.3)	52 (21.4)	138 (21.7)
Other	88 (55.7)	134 (56.8)	140 (57.6)	362 (56.8)
Missing	8 (5.1)	17 (7.2)	15 (6.2)	40 (6.3)

Age at Screening (years) as reported on CRF.
The denominator to calculate percentages is N, the number of participants in the full analysis set within each treatment group.
Data cutoff date: 06JAN2025

Table 21. Baseline and Disease Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Body Site, n (%)			
Colon, Ascending	46 (29.1)	78 (33.1)	72 (29.6)
Colon, Descending	15 (9.5)	18 (7.6)	16 (6.6)
Colon, Rectosigmoid	11 (7.0)	17 (7.2)	16 (6.6)
Colon, Sigmoid	25 (15.8)	30 (12.7)	32 (13.2)
Colon, Transverse	26 (16.5)	39 (16.5)	35 (14.4)
Colon, Hepatic Flexure	6 (3.8)	9 (3.8)	14 (5.8)
Colon, Splenic Flexure	1 (0.6)	1 (0.4)	7 (2.9)
Rectum	17 (10.8)	24 (10.2)	27 (11.1)
Cecum	11 (7.0)	20 (8.5)	24 (9.9)
Side of Tumor, n (%)			
Left	69 (43.7)	90 (38.1)	98 (40.3)
Right	89 (56.3)	146 (61.9)	145 (59.7)
Stage at Initial Diagnosis, n (%)			
Stage I	4 (2.5)	3 (1.3)	2 (0.8)
Stage II	7 (4.4)	13 (5.5)	10 (4.1)
Stage III	24 (15.2)	38 (16.1)	45 (18.5)
Stage IV	123 (77.8)	182 (77.1)	186 (76.5)
Primary Tumor Resection, n (%)			
Completely Resected	81 (51.3)	116 (49.2)	110 (45.3)
Partially Resected	9 (5.7)	14 (5.9)	11 (4.5)
No Resection	68 (43.0)	106 (44.9)	122 (50.2)
Number of Organs Involved, n (%)			
<= 2	86 (54.4)	119 (50.4)	127 (52.3)
>= 3	72 (45.6)	117 (49.6)	116 (47.7)
Presence of Liver Metastases, n (%)			
Yes	94 (59.5)	147 (62.3)	160 (65.8)
No	64 (40.5)	89 (37.7)	83 (34.2)
Liver Metastases only, n (%)			
Yes	13 (8.2)	24 (10.2)	30 (12.3)
Time Since Initial Diagnosis (months)			
Median (Range)	1.87 (0, 163)	1.94 (0, 112)	1.84 (0, 124)
Mean(SD)	7.91 (19.79)	6.81 (13.18)	7.26 (15.51)
Time Since Recurrence/Metastatic (months)			
Median (Range)	1.48 (0, 25)	1.54 (0, 40)	1.51 (0, 34)
Mean(SD)	2.14 (3.23)	2.26 (3.70)	2.03 (2.97)
ECOG PS at Baseline, n (%)			
0	79 (50.0)	128 (54.2)	131 (53.9)
1	74 (46.8)	104 (44.1)	98 (40.3)
Missing	5 (3.2)	4 (1.7)	14 (5.8)

Table 21. Baseline and Disease Characteristics - Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
BRAF V600E Status, Tumor Tissue (Central), n (%)			
Detected	150 (94.9)	226 (95.8)	224 (92.2)
Indeterminate	1 (0.6)	0	1 (0.4)
Not Detected	0	4 (1.7)	2 (0.8)
Not Available	7 (4.4)	6 (2.5)	16 (6.6)
BRAF V600E Status (Local), n (%)			
Detected	144 (91.1)	222 (94.1)	219 (90.1)
Not Detected	1 (0.6)	0	0
Not Available	13 (8.2)	14 (5.9)	24 (9.9)
KRAS Mutation Status (Local), n (%)			
Not Detected	152 (96.2)	231 (97.9)	229 (94.2)
Not Available	6 (3.8)	5 (2.1)	14 (5.8)
NRAS Mutation Status (Local), n (%)			
Not Detected	152 (96.2)	230 (97.5)	229 (94.2)
Not Available	6 (3.8)	6 (2.5)	14 (5.8)
MSI/MMR Status (Local), n (%)			
MSI-H/dMMR	0	1 (0.4)	0
MSS/pMMR	152 (96.2)	229 (97.0)	227 (93.4)
Not Available	6 (3.8)	6 (2.5)	16 (6.6)
CEA at Baseline (ug/L), n (%)			
<= 5 ug/L	50 (31.6)	64 (27.1)	63 (25.9)
> 5 ug/L	102 (64.6)	167 (70.8)	163 (67.1)
Missing	6 (3.8)	5 (2.1)	17 (7.0)
Median (Range)	12.80 (1, 3837)	13.60 (1, 6236)	17.35 (1, 11132)
Mean(SD)	160.0 (494.9)	149.9 (547.7)	226.0 (912.5)
CRP at Baseline (mg/L), n (%)			
<= 10 mg/L	91 (57.6)	125 (53.0)	118 (48.6)
> 10 mg/L	61 (38.6)	105 (44.5)	108 (44.4)
Missing	6 (3.8)	6 (2.5)	17 (7.0)
Median (Range)	6.75 (0, 289)	8.20 (0, 209)	8.50 (0, 284)
Mean(SD)	26.80 (43.35)	23.72 (36.09)	29.49 (44.05)

Number of organs and presence of liver metastases are based on BICR data for Phase 3.
Local testing can be performed by tumor or blood-based assays.
Local MSI status of MSS/pMMR includes MSI-L.
The last assessment prior to date of first dose of study intervention for ECOG and biomarker endpoints was used as baseline.
Data cutoff date: 06JAN2025

Pretreatment and subsequent anticancer treatments

The percentage of participants who received at least one prior adjuvant/neoadjuvant therapy was 14.8% EC + mFOLFOX6 arm and 13.2% control arm. Of these, 5.9% vs. 6.2% have received oxaliplatin alone, 6.8% vs. 5.4% have received oxaliplatin in combination and 6.8% vs. 4.1% have received capecitabine.

At the data cutoff date of 06 January 2025, a lower percentage of participants in the EC + mFOLFOX6 arm (45.8%) received at least one follow-up anticancer medication therapy compared with the control arm (57.2%). In the EC + mFOLFOX6 arm, the most frequent (≥5% of participants) follow-up anticancer medication therapies by drug category were FOLFIRI ± combination (24.2%), BRAF inhibitor ± combination (8.1%), and single-agent chemotherapy ± combination (7.2%). In the control arm, the most frequent (≥5% of participants) follow-up anticancer medication therapies by drug category were BRAF inhibitor ± combination (41.2%), FOLFIRI ± combination (16.5%), single-agent chemotherapy ± combination (7.8%), and trifluridine/tipiracil ± VEGF inhibitor (5.8%).

Duration of treatment

The median duration of exposure to study treatment was 49.8 weeks (range: 1.3 to 161.9 weeks) in the EC + mFOLFOX6 Arm (N=232) and 25.9 weeks (range: 2.0 to 150.0 weeks) in the Control Arm (N=229), with 28.4%, and 6.6% of participants, respectively, still receiving study treatment at the time of the data cutoff; 41.4% of participants in EC + mFOLFOX6 Arm and 10.9% of participants in the Control Arm received ≥60 weeks of study treatment.

The median duration of exposure to oxaliplatin was 21.3 weeks (range: 1.3 to 141.1 weeks) in the EC + mFOLFOX6 Arm, shorter than the median duration of the overall study treatment: 49.8 weeks (range: 1.3 to 161.9 weeks). In the Control Arm, median duration of exposure to oxaliplatin was 19.0 weeks (range: 2.0 to 98.3 weeks) vs 25.9 weeks (range: 2.0 to 150.0 weeks) for the overall duration of the overall study treatment.

Table 22 Duration of Treatment (Study) - Phase 3 Safety Set

	EC (N=153)			EC+mFOLFOX6 (N=232)						Control (N=229)						
	Encorafenib (N=152)	Cetuximab (N=153)	Regimen (N=153)	Encorafenib (N=232)	Cetuximab (N=232)	Fluorouracil (N=232)	Leucovorin (N=232)	Oxaliplatin (N=232)	Regimen (N=232)	Fluorouracil (N=182)	Leucovorin (N=180)	Irinotecan (N=67)	Oxaliplatin (N=229)	Capecitabine (N=47)	Bevacizumab (N=197)	Regimen (N=229)
Duration of Treatment (weeks)																
n	152	153	153	232	232	232	232	232	232	182	180	67	229	47	197	229
Mean (SD)	39.59 (34.36)	39.45 (34.28)	39.68 (34.27)	54.31 (36.21)	53.81 (36.18)	46.73 (34.14)	46.53 (34.38)	23.25 (15.96)	55.45 (35.41)	31.26 (24.29)	30.39 (23.55)	35.01 (27.46)	20.17 (13.86)	28.75 (27.14)	30.81 (24.84)	30.88 (24.83)
Q1	19.0	19.1	19.1	23.9	23.9	20.1	19.9	15.3	26.1	14.0	13.9	16.0	11.0	8.9	12.9	13.1
Median (range)	27.00 (0.14, 153.00)	26.29 (2.00, 153.57)	27.00 (2.00, 153.57)	49.43 (0.43, 161.86)	49.07 (1.29, 160.71)	37.50 (1.29, 160.71)	36.71 (1.29, 160.71)	21.29 (1.29, 141.14)	49.79 (1.29, 161.86)	26.50 (2.00, 150.00)	25.93 (2.00, 150.00)	30.00 (2.00, 150.00)	19.00 (2.00, 98.29)	18.00 (2.71, 130.86)	25.86 (2.00, 150.00)	25.86 (2.00, 150.00)
Q3	47.9	46.0	47.9	78.1	77.5	68.1	68.1	27.1	79.5	38.3	37.8	42.9	25.1	39.6	38.9	39.0
Category (weeks)																
< 4	6 (3.9)	6 (3.9)	6 (3.9)	7 (3.0)	6 (2.6)	9 (3.9)	11 (4.7)	10 (4.3)	3 (1.3)	8 (4.4)	7 (3.9)	1 (1.5)	14 (6.1)	5 (10.6)	11 (5.6)	12 (5.2)
>= 4 - < 12	10 (6.6)	12 (7.8)	11 (7.2)	19 (8.2)	22 (9.5)	18 (7.8)	18 (7.8)	27 (11.6)	14 (6.0)	30 (16.5)	32 (17.8)	8 (11.9)	46 (20.1)	8 (17.0)	30 (15.2)	38 (16.6)
>= 12 - < 24	46 (30.3)	43 (28.1)	42 (27.5)	33 (14.2)	30 (12.9)	42 (18.1)	42 (18.1)	104 (44.8)	35 (15.1)	39 (21.4)	39 (21.7)	17 (25.4)	93 (40.6)	14 (29.8)	46 (23.4)	53 (23.1)
>= 24 - < 36	32 (21.1)	34 (22.2)	36 (23.5)	27 (11.6)	28 (12.1)	42 (18.1)	41 (17.7)	65 (28.0)	29 (12.5)	48 (26.4)	49 (27.2)	14 (20.9)	60 (26.2)	5 (10.6)	48 (24.4)	54 (23.6)
>= 36 - < 48	20 (13.2)	21 (13.7)	20 (13.1)	27 (11.6)	26 (11.2)	26 (11.2)	26 (11.2)	14 (6.0)	29 (12.5)	24 (13.2)	23 (12.8)	13 (19.4)	6 (2.6)	5 (10.6)	24 (12.2)	29 (12.7)
>= 48 - < 60	9 (5.9)	9 (5.9)	9 (5.9)	25 (10.8)	26 (11.2)	24 (10.3)	22 (9.5)	4 (1.7)	26 (11.2)	14 (7.7)	12 (6.7)	6 (9.0)	6 (2.6)	5 (10.6)	14 (7.1)	18 (7.9)
>= 60	29 (19.1)	28 (18.3)	29 (19.0)	94 (40.5)	94 (40.5)	71 (30.6)	72 (31.0)	8 (3.4)	96 (41.4)	19 (10.4)	18 (10.0)	8 (11.9)	4 (1.7)	5 (10.6)	24 (12.2)	25 (10.9)
Category (months)																
>=6	78 (51.3)	78 (51.0)	79 (51.6)	169 (72.8)	168 (72.4)	152 (65.5)	150 (64.7)	67 (28.9)	174 (75.0)	92 (50.5)	89 (49.4)	35 (52.2)	50 (21.8)	19 (40.4)	96 (48.7)	112 (48.9)
>=12	34 (22.4)	34 (22.2)	34 (22.2)	111 (47.8)	111 (47.8)	87 (37.5)	87 (37.5)	11 (4.7)	113 (48.7)	27 (14.8)	25 (13.9)	12 (17.9)	9 (3.9)	8 (17.0)	32 (16.2)	35 (15.3)

Duration of treatment (weeks) = (last dose – first dose + 1)/7 for encorafenib, (last dose – first dose + 14)/7 for cetuximab, FOLFIRI, mFOLFOX6 taken every two weeks on 28-day cycle, (last dose – first dose + 21)/7 for oxaliplatin taken every three weeks on 21-day cycle, (last dose – first dose + 7)/7 for capecitabine.
Duration of treatment (months) = Duration in days/30.4375.
Not all participants started treatment with all agents.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2025 (17:03) Source Data: adexsum Table Generation: 13FEB2025 (11:52)
(Data cutoff date : 06JAN2025 Database snapshot date : 27JAN2025) Output File: ./C4221015 P3 PFS PCD/C4221015_20250127_Unblinded/adexsum_s002_p3
Table 14.4.1.1.1 encorafenib is for Pfizer internal use.

Dose intensity

The median relative dose intensity in the EC + mFOLFOX6 Arm was between 80.0% (49.9% to 102.5%) for 5-FU to 92.6% (range: 38.4% to 117.3%) for cetuximab. Relative dose intensity for encorafenib was 89.9% (range: 3.0% to 100.0%). In the control arm, the median relative dose intensity was between 99.3 % for bevacizumab and 68.6% for capecitabine.

Table 23 Dose intensity (study) - Phase 3 Safety Set (Protocol C4221015)

	EC (N=153)		EC+mFOLFOX6 (N=232)					Control (N=229)					
	Encorafenib (N=152)	Cetuximab (N=153)	Encorafenib (N=232)	Cetuximab (N=232)	Fluorouracil (N=232)	Leucovorin (N=232)	Oxaliplatin (N=232)	Fluorouracil (N=182)	Leucovorin (N=180)	Irinotecan (N=67)	Oxaliplatin (N=229)	Capecitabine (N=47)	Bevacizumab (N=197)
Cumulative dose[a]													
n	152	152	232	231	231	231	231	181	179	66	226	45	197
Mean (SD)	78134.7 (67697.83)	9370.3 (8299.10)	101387.7 (69862.99)	12030.5 (8436.95)	50586.2 (38206.41)	7773.0 (6172.66)	726.9 (403.43)	35208.6 (28522.91)	5193.2 (4044.61)	2362.4 (2068.19)	696.1 (460.50)	214049.1 (201151.42)	71.5 (62.67)
Q1	36675.0	4490.9	43950.0	5027.2	20058.1	3199.4	498.6	15943.4	2131.6	1154.8	383.3	77380.7	30.0
Median (range)	54000.0 (300.0, 314700.0)	6506.9 (0.0, 38389.5)	89850.0 (900.0, 324900.0)	10618.9 (199.0, 38211.5)	39219.6 (2440.8, 193647.0)	5824.5 (174.3, 30569.2)	686.7 (68.5, 3332.8)	29399.9 (2767.8, 225496.2)	4540.3 (395.1, 21141.7)	1720.2 (173.5, 11626.6)	677.8 (63.5, 4184.1)	156805.7 (14623.5, 883498.3)	60.0 (4.6, 490.2)
Q3	93900.0	10522.5	148500.0	17667.1	75153.1	11346.8	898.2	42716.4	6800.1	2779.9	908.7	269731.2	89.7
Dose Intensity[b]													
n	152	152	232	231	231	231	231	181	179	66	226	45	197
Mean (SD)	284.1 (28.33)	33.1 (6.22)	264.8 (45.54)	31.7 (4.17)	157.9 (28.16)	24.0 (4.97)	4.8 (0.91)	165.5 (30.42)	24.7 (4.65)	9.4 (1.72)	5.1 (0.89)	1134.3 (216.65)	0.3 (0.07)
Q1	281.7	32.7	245.2	29.9	138.3	22.9	4.2	145.5	22.9	8.3	4.6	961.8	0.3
Median (range)	299.3 (164.7, 301.2)	35.0 (0.0, 37.2)	284.2 (90.0, 300.0)	32.2 (13.4, 56.6)	159.5 (95.4, 317.0)	25.4 (8.9, 45.3)	4.7 (1.9, 9.6)	168.2 (97.8, 246.5)	26.3 (11.6, 30.8)	9.4 (5.3, 12.6)	5.3 (2.2, 6.8)	1145.5 (630.8, 1493.4)	0.3 (0.2, 0.7)
Q3	300.0	35.8	299.1	34.4	175.4	27.0	5.4	189.6	27.9	10.7	5.9	1319.0	0.4
Relative Dose Intensity (%)[c]													
n	152	152	232	231	231	231	231	181	179	66	226	45	197
Mean (SD)	90.8 (14.15)	94.6 (17.74)	81.8 (20.66)	90.7 (10.75)	79.7 (13.45)	91.4 (11.81)	82.6 (18.29)	86.0 (13.53)	94.4 (15.13)	81.9 (14.89)	89.1 (19.86)	66.9 (18.24)	93.7 (16.68)
Q1	87.7	95.2	73.2	85.5	69.7	85.7	71.6	77.3	88.3	72.5	79.3	54.1	87.0
Median (range)	96.9 (13.6, 102.4)	99.4 (0.0, 114.1)	89.9 (3.0, 100.0)	92.6 (38.4, 117.3)	80.0 (49.9, 102.5)	92.5 (48.3, 166.9)	82.6 (30.5, 201.9)	88.0 (50.2, 116.5)	96.1 (53.4, 200.5)	81.3 (46.7, 120.5)	90.3 (42.2, 204.9)	68.6 (22.2, 98.7)	97.7 (33.1, 201.9)
Q3	99.4	100.9	97.1	97.8	88.7	99.1	95.0	98.5	100.0	93.6	99.7	80.3	100.1
< 50%	2 (1.3)	7 (4.6)	23 (9.9)	3 (1.3)	3 (1.3)	2 (0.9)	6 (2.6)	1 (0.5)	1 (0.6)	3 (4.5)	5 (2.2)	11 (23.4)	1 (0.5)
50% - < 75%	20 (13.2)	2 (1.3)	40 (17.2)	17 (7.3)	73 (31.5)	18 (7.8)	70 (30.2)	39 (21.4)	12 (6.7)	18 (26.9)	43 (18.8)	20 (42.6)	15 (7.6)
75% - < 90%	20 (13.2)	13 (8.5)	53 (22.8)	74 (31.9)	105 (45.3)	70 (30.2)	84 (36.2)	65 (35.7)	43 (23.9)	25 (37.3)	66 (28.8)	11 (23.4)	42 (21.3)
90% - < 110%	110 (72.4)	125 (81.7)	116 (50.0)	135 (58.2)	51 (22.0)	138 (59.5)	69 (29.7)	75 (41.2)	120 (66.7)	20 (29.9)	108 (47.2)	5 (10.6)	134 (68.0)
>= 110%	0	6 (3.9)	0	3 (1.3)	0	4 (1.7)	3 (1.3)	2 (1.1)	4 (2.2)	1 (1.5)	7 (3.1)	0	5 (2.5)

a. Cumulative dose= sum of all administered doses. In mg for encorafenib, in mg/m2 for cetuximab, irinotecan, oxaliplatin, leucovorin, fluorouracil, and capecitabine, in mg/kg for bevacizumab.
b. Dose intensity = cumulative dose / duration of treatment (days). In mg/day for encorafenib, in mg/m2/day for cetuximab, irinotecan, oxaliplatin, leucovorin, fluorouracil, and capecitabine, in mg/kg/day for bevacizumab.
c. Relative dose intensity = 100 * (cumulative dose / planned cumulative dose). Planned cumulative is sum of all doses assuming all doses administered at the protocol-specified dose.
Not all patients started treatment with all agents.
PFIZER CONFIDENTIAL SDTM Creation: 27JAN2025 (17:03) Source Data: adexsum Table Generation: 13FEB2025 (11:52)
(Data cutoff date : 06JAN2025 Database snapshot date : 27JAN2025) Output File: ./C4221015 P3 PFS PCD/C4221015_20250127_Unblinded/adexsum_s007_p3
Table 14.4.1.2.1 encorafenib is for Pfizer internal use.

Dose modification and reductions

In the EC + mFOLFOX6 arm, 29.7% of patients had at least one dose reduction of encorafenib and 12.9% had at least one dose reduction of cetuximab. AEs were the most common reason for dose reductions of encorafenib and cetuximab. Furthermore, 72.8% of participants had at least one dose interruption of encorafenib and 80.2% had at least one dose interruption of cetuximab. The comparison of oxaliplatin, the only agent administered in the treatment arm and all regimes of the control arm, shows for both, dose reductions (67.2% vs 54.6%) and dose interruptions (72.0% vs 51.1%) higher rates in the treatment arm compared to the control arm, respectively.

Numbers analysed

Table 24 Summary of Analysis Sets - Phase 3 Full Analysis Set (Protocol C4221015)

Analysis Set Category	EC (N=158) n (%)	EC+mFOLFOX6 (N=236) n (%)	Control (N=243) n (%)
Screened	1047		
Randomized to Treatment	158 (100.0)	236 (100.0)	243 (100.0)
Not Treated	5 (3.2)	4 (1.7)	14 (5.8)
Full Analysis Set	158 (100.0)	236 (100.0)	243 (100.0)
Safety Analysis Set	153 (96.8)	230 (97.5)	229 (94.2)
Central BRAF V600E Positive Analysis Set	153 (96.8)	232 (98.3)	229 (94.2)
ORR Subset	0	110 (46.6)	110 (45.3)
PK Analysis Set	144 (91.1)	214 (90.7)	0
PK Concentration Analysis Set	144 (91.1)	214 (90.7)	0
PK Parameters Analysis Set	12 (7.6)	27 (11.4)	0
Biomarker Analysis Set	153 (96.8)	232 (98.3)	229 (94.2)
Tumor Tissue Analysis Set	159 (98.1)	227 (96.2)	222 (91.4)
ctDNA Analysis Set	147 (93.0)	225 (95.3)	220 (90.5)
Paired ctDNA Analysis Set	139 (87.9)	217 (91.9)	215 (88.5)
ctDNA Diagnostics Concord. Analysis Set	145 (91.8)	223 (94.5)	215 (88.5)

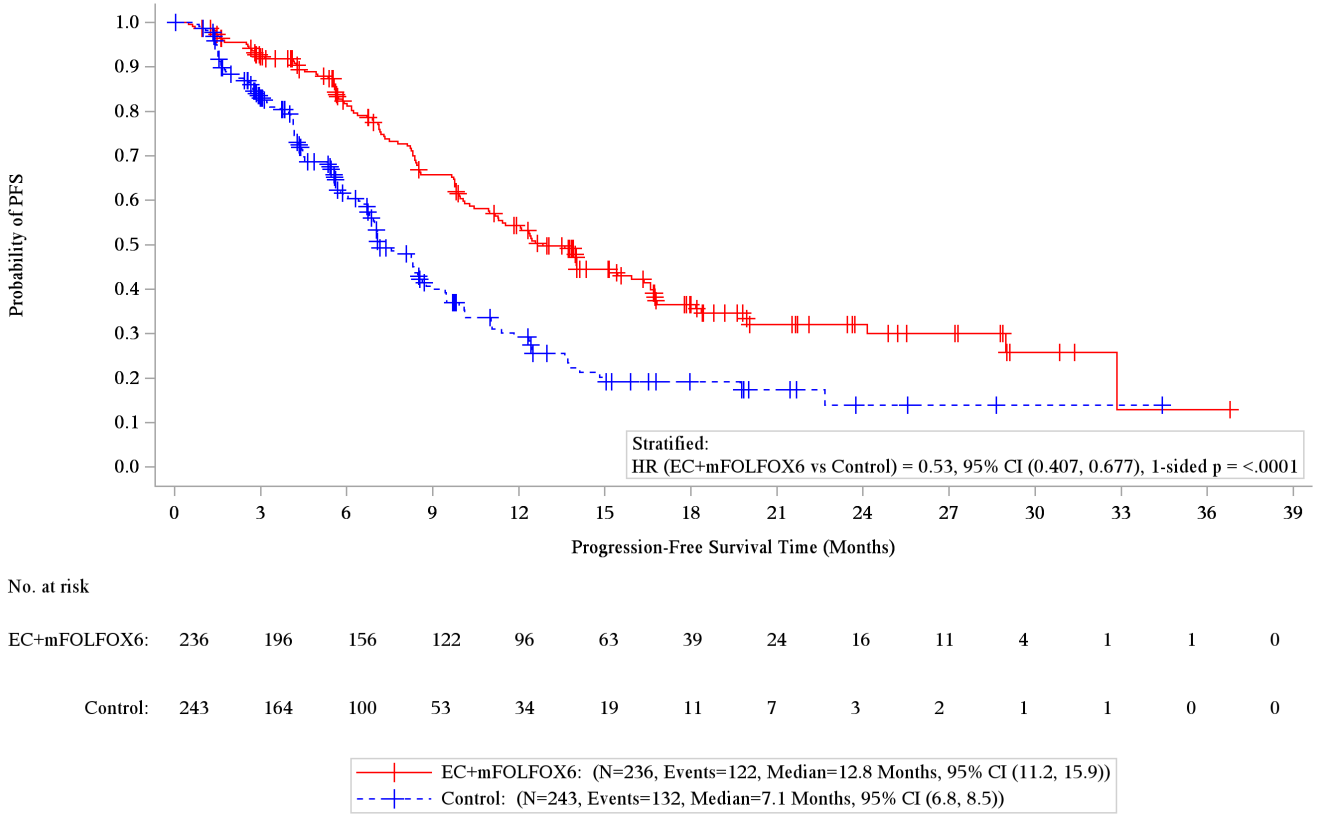
Full Analysis Set: all randomized. Safety Analysis Set: randomized and received ⩾1 dose, summarised by treatment received. Central BRAF V600E Set: BRAF-positive by central lab. ORR Subset: first 110 randomized per arm; totals may exceed 110 if multiple randomizations occurred on the same day. PK Analysis Sets: Safety Set participants with PK concentration >0 and/or PK parameter data without major deviations. Biomarker Set: ⩾ 1 biomarker assessment at baseline/post-baseline. Tumor Tissue Set: baseline tumor tissue sample collected. ctDNA Sets: baseline ctDNA sample and/or baseline + post-baseline ctDNA samples collected by central lab. ctDNA Concordance Set: baseline tumor tissue + baseline ctDNA available.

Outcomes and estimation

Primary (dual) efficacy endpoint PFS by BICR

The study met its primary endpoint of demonstrating statistically significant prolonged PFS by BICR for the EC+mFOLFOX6 arm compared with the control arm. After a median duration of follow-up of 16.8 months (Arm B, 95% CI: 15.1, 18.4) vs 9.8 months (control arm, 95% CI: 8.5, 13.0), median PFS by BICR was 12.8 months (95% CI: 11.2, 15.9) vs 7.1 months (95% CI: 6.8, 8.5) in the EC+mFOLFOX6 arm vs control arm, respectively.

Figure 8 KM Plot of PFS (Primary Analysis) Based on BICR Assessment (RECIST v1.1) - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)



CI based on the Brookmeyer and Crowley method. Stratified by ECOG PS and Region. Hazard ratio based on Cox proportional hazards model; under proportional hazards, hazard ratio < 1 indicates a reduction in hazard rate in favour of EC+mFOLFOX6 compared to Control. p-value based on stratified log-rank test. Data cutoff date: 06JAN2025,

Table 25 PFS Based on BICR Assessment (RECIST v1.1) – Primary analysis Phase 3 Full Analysis Set

Category	EC+mFOLFOX6 (N=236)	Control (N=243)
Participants with event, n (%)	122 (51.7)	132 (54.3)
Progressive disease	105 (44.5)	109 (44.9)
Death	17 (7.2)	23 (9.5)
Participants censored, n (%)	114 (48.3)	111 (45.7)
No adequate baseline assessment	4 (1.7)	2 (0.8)
Start of new anti-cancer therapy	53 (22.5)	63 (25.9)
Event after ≥2 missing post-baseline assessments	4 (1.7)	11 (4.5)
Withdrawal of consent	5 (2.1)	14 (5.8)
Lost to follow-up	1 (0.4)	1 (0.4)
No adequate post-baseline tumour assessment	0	0
Ongoing without an event	47 (19.9)	20 (8.2)
Probability of being event-free (95% CI) at 3 months	0.923 (0.879, 0.951)	0.830 (0.772, 0.875)
at 6 months	0.817 (0.758, 0.864)	0.610 (0.537, 0.675)
at 9 months	0.658 (0.586, 0.719)	0.399 (0.323, 0.474)
at 12 months	0.543 (0.469, 0.610)	0.293 (0.220, 0.368)
at 15 months	0.444 (0.371, 0.515)	0.202 (0.136, 0.278)
at 18 months	0.365 (0.291, 0.439)	0.192 (0.127, 0.267)
at 21 months	0.321 (0.245, 0.399)	0.174 (0.109, 0.252)
Kaplan–Meier estimates of Time to Event (months)		
Q1, months (95% CI)	7.2 (6.2, 8.4)	4.2 (3.9, 5.3)
Median, months (95% CI)	12.8 (11.2, 15.9)	7.1 (6.8, 8.5)
Q3, months (95% CI)	32.9 (20.0, NE)	13.6 (11.1, 19.7)
Stratified analysis – Comparison vs Control		
Hazard ratio	0.53	
95% CI	0.407, 0.677	
1-sided p-value	<.0001	
2-sided p-value	<.0001	

Hazard ratio <1 favours EC+mFOLFOX6 vs Control. CIs derived using log–log transformation; stratified by ECOG PS, randomization and geographic region.

Sensitivity analyses:

An unstratified Cox regression analysis of PFS by BICR yielded a hazard ratio of 0.51 (95% CI: 0.395–0.652; p<0.001), consistent with the primary estimate. A stratified analysis of PFS by BICR conducted in the Central BRAF V600E Positive Analysis Set demonstrated a hazard ratio of 0.53 (95% CI: 0.411–0.689; p<0.001).

As Schoenfeld's residual test indicated deviation from the proportional hazards assumption for the stratified Cox model, a restricted mean survival time (RMST) analysis was performed. Using τ_1 = 34.43 months, RMST estimates were 16.93 months (95% CI: 15.118–18.737) for EC+mFOLFOX6 and 11.31 months (95% CI: 9.449–13.180) for the control arm, corresponding to an RMST difference of 5.61 months (95% CI: 3.014–8.211; two-sided p<0.0001) in favour of EC+mFOLFOX6.

Multivariate Cox regression analysis showed that geographic region (US/CAN vs EUROPE vs ROW) does not have a significant impact on the primary endpoint. Furthermore, a higher risk of progression or death was observed in patients with less than 3 organs involved at baseline and patients with liver metastases at baseline.

Supplementary analyses

A stratified treatment-policy analysis of PFS by BICR, incorporating events occurring after initiation of subsequent anticancer therapy, resulted in a hazard ratio of 0.52 (95% CI: 0.409–0.657), with median PFS of 12.5 months (95% CI: 10.4–15.2) versus 7.1 months (95% CI: 6.8–8.5) in the control arm.

Similarly, a stratified analysis disregarding the timing gap criterion (i.e. including events occurring >12 or >16 weeks after the last adequate post-baseline tumour assessment) produced a hazard ratio of 0.53 (95% CI: 0.412–0.673), and a median PFS of 12.6 months (95% CI: 10.9–15.4) versus 7.1 months (95% CI: 6.8–8.6), consistent with the primary result.

Effect estimates across clinically relevant subgroups are summarised below.

Figure 9 Forest Plot of PFS Based on BICR Assessment (RECIST v1.1) - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)

Subgroup	Number of Participants, n (%) EC+mFOLFOX6	Control	Number of Events/ Number of Participants (N) EC+mFOLFOX6	Control	Hazard Ratio (95% CI)
All participants (stratified)	236 (100.0)	243 (100.0)	122/236	132/243	0.53 (0.407, 0.677)
All participants (unstratified)	236 (100.0)	243 (100.0)	122/236	132/243	0.51 (0.395, 0.652)
Age:					
<65	150 (63.6)	139 (57.2)	78/150	71/139	0.51 (0.365, 0.710)
>=65	86 (36.4)	104 (42.8)	44/86	61/104	0.51 (0.344, 0.754)
Sex:					
Male	123 (52.1)	119 (49.0)	59/123	63/119	0.50 (0.349, 0.721)
Female	113 (47.9)	124 (51.0)	63/113	69/124	0.53 (0.371, 0.746)
ECOG:					
0	131 (55.5)	136 (56.0)	60/131	74/136	0.43 (0.302, 0.608)
1	105 (44.5)	107 (44.0)	62/105	58/107	0.63 (0.436, 0.902)
No. of organs involved at Baseline:					
<= 2	119 (50.4)	127 (52.3)	52/119	66/127	0.40 (0.276, 0.580)
>= 3	117 (49.6)	116 (47.7)	70/117	66/116	0.64 (0.452, 0.895)
Side of tumor:					
Left	90 (38.1)	98 (40.3)	51/90	53/98	0.49 (0.326, 0.726)
Right	146 (61.9)	145 (59.7)	71/146	79/145	0.52 (0.374, 0.717)
Liver metastases at Baseline per BICR:					
Yes	147 (62.3)	160 (65.8)	87/147	86/160	0.60 (0.441, 0.807)
No	89 (37.7)	83 (34.2)	35/89	46/83	0.36 (0.228, 0.573)

Data cutoff date: 06JAN2025

Subgroup analysis according to choice of regimen in the control arm

A subgroup analysis for PFS by BICR for EC+mFOLFOX6 and each regimen of the control arm showed a consistent result, with differing numerical effect sizes. At the time of the PFS PCD, the hazard ratios for PFS by BICR estimated using a Cox regression model stratified by ECOG PS and Geographic Region were:

- EC + mFOLFOX6 Arm vs mFOLFOX6 + bevacizumab regimen: 0.45 (95%CI: 0.322; 0.619)
- EC + mFOLFOX6 Arm vs FOLFOXIRI + bevacizumab regimen: 0.87 (95%CI: 0.544; 1.386)

- EC + mFOLFOX6 Arm vs CAPOX + bevacizumab regimen: 0.40 (95%CI: 0.260; 0.613)
- EC + mFOLFOX6 Arm vs mFOLFOX6 regimen: 0.25 (95%CI: 0.130, 0.48).

The treatment effect is also consistently present in other important subgroups, see Figure 10.

Secondary Endpoint PFS by Derived Investigator Assessment (PFS INV)

The stratified HR for PFS by derived Investigator assessment for the EC + mFOLFOX6 arm vs the control arm was 0.44 (95% CI: 0.349, 0.564). The overall PFS discrepancy rate between BICR and derived Investigator assessment was 20.8% for the EC + mFOLFOX6 Arm and 13.2% for the Control Arm.

Results of the PFS by INV analysis are provided below.

Table 26 Summary of PFS Based on Derived Investigator Assessment (RECIST v1.1)

Category	EC+mFOLFOX6 (N=236)	Control (N=243)
Participants with event, n (%)	133 (56.4)	160 (65.8)
Progressive disease	117 (49.6)	140 (57.6)
Death	16 (6.8)	20 (8.2)
Participants censored, n (%)	103 (43.6)	83 (34.2)
No adequate baseline assessment	0	0
Start of new anti-cancer therapy	38 (16.1)	41 (16.9)
Event after ≥2 missing post-baseline assessments	4 (1.7)	10 (4.1)
Withdrawal of consent	5 (2.1)	13 (5.3)
Lost to follow-up	1 (0.4)	1 (0.4)
No adequate post-baseline tumour assessment	0	0
Ongoing without an event	55 (23.3)	18 (7.4)
Probability event-free (95% CI) at 3 months	0.932 (0.890, 0.959)	0.815 (0.757, 0.861)
at 6 months	0.825 (0.766, 0.870)	0.575 (0.503, 0.640)
at 9 months	0.697 (0.628, 0.755)	0.362 (0.293, 0.431)
at 12 months	0.571 (0.499, 0.636)	0.263 (0.199, 0.331)
at 15 months	0.460(0.388, 0.529)	0.173 (0.117, 0.237)
at 18 months	0.376 (0.304, 0.448)	0.116 (0.069, 0.175)
at 21 months	0.315 (0.248, 0.389)	0.106 (0.061, 0.165)
Kaplan–Meier Quartiles (95% CI)		
Q1	7.8 (6.7, 9.7)	4.2 (3.6, 4.7)
Median	13.6 (12.1, 16.1)	7.0 (6.0, 8.3)
Q3	25.2 (19.9, NE)	12.3 (10.1, 14.1)
Stratified analysis – Comparison vs Control		
Hazard Ratio	0.44	
95% CI	0.349–0.564	
1-sided p-value	<0.0001	
2-sided p-value	<0.0001	

CIs derived by log–log transformation; Brookmeyer–Crowley for medians. Stratified by ECOG PS, region and randomization. HR <1 favours EC+mFOLFOX6.

Primary (dual) endpoint ORR by BICR

The primary analysis for ORR was performed at the time of the ORR PCD (22 Dec 23) in the ORR subset (Table 27).

Table 27 Summary of Best Overall Response and ORR (Confirmed) Based on BICR Assessment (RECIST v1.1) - Phase 3 EC+mFOLFOX6 and Control Arms ORR Subset Full Analysis Set

Category	EC+mFOLFOX6 (N=110)	Control (N=110)
Confirmed Best Overall Response, n (%)		
Complete response	3 (2.7)	2 (1.8)
Partial response	64 (58.2)	42 (38.2)
Stable disease	31 (28.2)	34 (30.9)
Non-CR/Non-PD	3 (2.7)	4 (3.6)
Progressive disease	3 (2.7)	9 (8.2)
Not evaluable	6 (5.5)	19 (17.3)
Reason for Not Evaluable, n (%)		
No adequate baseline assessment	0	2 (1.8)
No post-baseline assessments due to early death	2 (1.8)	5 (4.5)
No post-baseline assessments due to other reasons	4 (3.6)	9 (8.2)
Stable disease too early (<6 weeks after randomization)	0	3 (2.7)
Objective Response (CR + PR), n (%)	67 (60.9)	44 (40.0)
95% CI	51.6–69.5	31.3–49.3
Stratified Analysis of ORR (EC+mFOLFOX6 vs Control)		
Odds ratio	2.443	
95% CI	1.348–4.380	
99.8% CI	0.989–6.089	
1-sided p-value	0.0008	
2-sided p-value	0.0015	

Odds ratio estimated via Mantel–Haenszel method stratified by ECOG PS and geographic region. Odds ratio >1 indicates improved ORR for EC+mFOLFOX6 compared to Control. Exact confidence intervals calculated using Wilson method. p-values derived from Cochran–Mantel–Haenszel (CMH) test.

An additional descriptive ORR analysis was conducted at the time of the PFS PCD analysis (06 Jan 25) Confirmed ORR by BICR in the EC + mFOLFOX6 Arm (65.7% [95% CI: 59.4%, 71.4%]) was higher than that in the Control Arm (37.4% [95% CI: 31.6%, 43.7%] Table 28).

Table 28 Summary of Best Overall Response and ORR (Confirmed) Based on BICR Assessment (RECIST v1.1) Phase 3 Full Analysis Set (Protocol C4221015)

Category	EC (N=158)	EC+mFOLFOX6 (N=236)	Control (N=243)
Confirmed Best Overall Response, n (%)			
Complete response	3 (1.9)	11 (4.7)	8 (3.3)
Partial response	69 (43.7)	144 (61.0)	83 (34.2)
Stable disease	57 (36.1)	50 (21.6)	83 (35.0)
Non-CR/Non-PD	7 (4.4)	5 (1.2)	9 (3.7)
Progressive disease	12 (7.6)	8 (3.4)	21 (8.6)
Not evaluable	10 (6.3)	18 (7.6)	37 (15.2)
Reasons for Not Evaluable, n (%)			
No adequate baseline assessment	0	4 (1.7)	2 (0.8)
No post-baseline assessments due to early death	1 (0.6)	3 (1.3)	11 (4.5)
No post-baseline assessments due to other reasons	8 (5.1)	7 (3.0)	16 (6.6)
New anti-cancer therapy before first post-baseline assessment	1 (0.6)	1 (0.4)	2 (0.8)
Stable disease too early	0	3 (1.3)	5 (1.2)
Progressive disease too late (>12 weeks after randomization)	0	0	1 (0.4)
Objective Response (CR+PR), n (%)	72 (45.6)	155 (65.7)	91 (37.4)
95% CI	38.0–53.3	59.4–71.4	31.6–43.7

CI calculated using Wilson method. ORR based on confirmed CR+PR. Data cutoff: 06 JAN 2025.

For patients who responded, duration of response was 9.2 (1.3, 35.2) in the treatment arm and 5.5 (1.0, 32.9) month in the control arm. A sensitivity analysis based on the Central BRAF V600E Positive Analysis Set yielded ORR values similar to those of the ORR analysis based on the FAS. An analysis for the predefined secondary endpoint ORR by INV was concordant to the results of the ORR by BICR analysis.

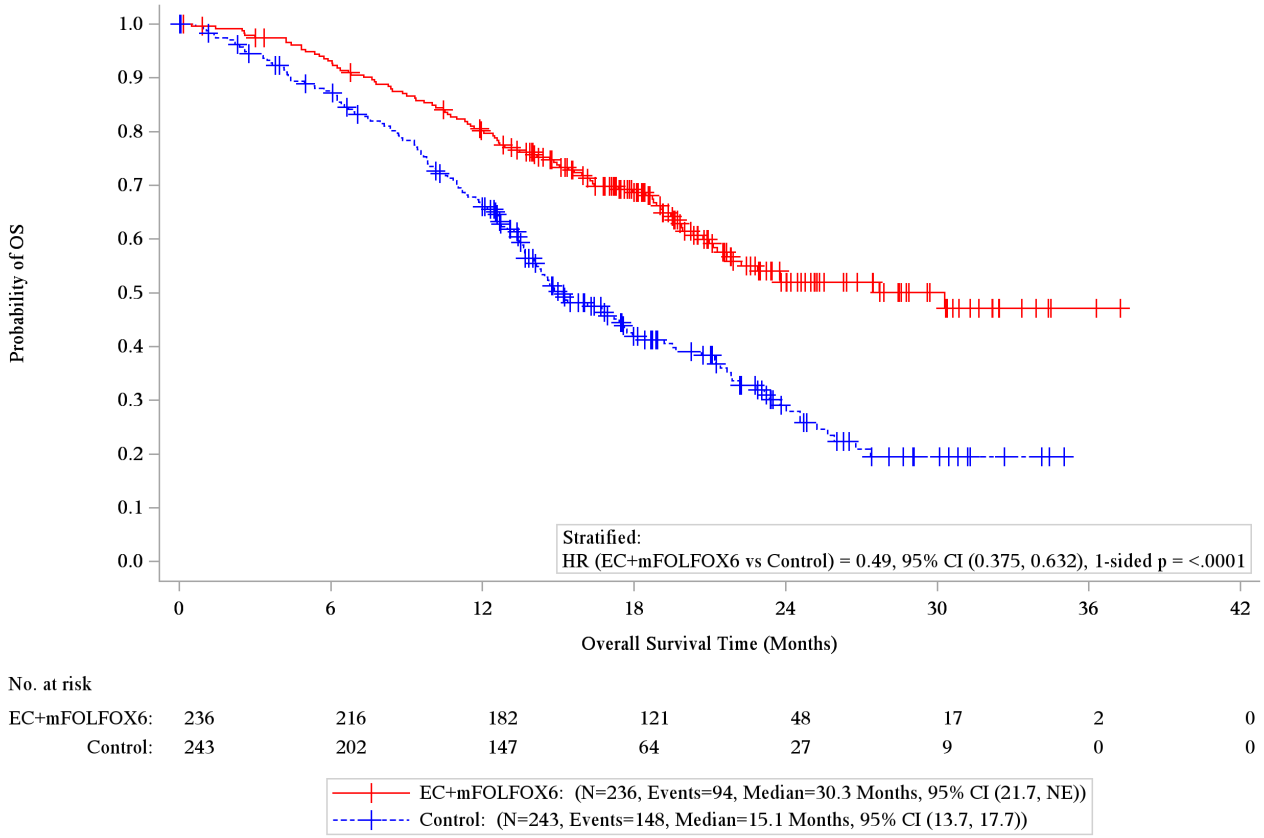
Key secondary endpoint Overall Survival

The median duration of follow-up for OS was 21.8 months (95% CI: 20.4, 23.4) for participants in the EC + mFOLFOX6 arm and 22.2 months (95% CI: 18.9, 23.5) for participants in the control arm. A total of 242 OS events (81.5% information fraction) had occurred at the time of the data cutoff, with deaths occurring in 94 (39.8%) participants in the EC + mFOLFOX6 arm and 148 (60.9%) participants in the control arm. Median OS was 30.3 months (95% CI: 21.7, NE) for participants in the EC + mFOLFOX6 arm and 15.1 months (95% CI: 13.7, 17.7) for participants in the control arm. The HR for death was 0.49 (95% CI: 0.375, 0.632, RCI: 0.36, 0.658, 1-sided p-value <0.0001) See Figure 11 and Table 29.

Sensitivity analyses including an unstratified analysis of OS (HR 0.48, 95% CI: 0.371, 0.623), a stratified analysis based on the central BRAF V600E positive analysis set (HR 0.50; 0.381, 0.646),

RMST analysis (RMST difference 6.57 (4.358, 8.780)) and a multivariate Cox regression analysis generally support the primary finding.

Figure 11 KM Plot of Overall Survival - Phase 3 EC+mFOLFOX6 and Control Arms Full Analysis Set (Protocol C4221015)



Data cutoff date: 06JAN2025

Table 29 Summary of Overall Survival – Phase 3 EC+mFOLFOX6 and Control Arms, Full Analysis Set (Protocol C4221015)

Category	EC+mFOLFOX6 (N=236)	Control (N=243)
Participants with event, n (%)	94 (39.8)	148 (60.9)
Participants censored, n (%)	142 (60.2)	95 (39.1)
Withdrawal of consent	8 (3.4)	17 (7.0)
Lost to follow-up	2 (0.8)	1 (0.4)
Alive	132 (55.9)	77 (31.7)
Probability of being event-free (95% CI)		
at 6 months	0.931 (0.890, 0.957)	0.876 (0.826, 0.912)
at 12 months	0.801 (0.744, 0.847)	0.660 (0.594, 0.717)
at 18 months	0.687 (0.621, 0.744)	0.419 (0.350, 0.487)
at 24 months	0.520 (0.439, 0.594)	0.290 (0.221, 0.363)
at 30 months	0.500 (0.414, 0.580)	0.195 (0.128, 0.273)
at 36 months	0.471 (0.372, 0.563)	NE (NE, NE)
Kaplan–Meier estimates of Time to Event (months)		
Q1	14.7 (11.9, 17.9)	9.8 (8.6, 11.2)
Median	30.3 (21.7, NE)	15.1 (13.7, 17.7)
Q3	NE (NE, NE)	25.2 (22.9, NE)
Stratified analysis		
Hazard Ratio	0.49	
95% Cie	0.375, 0.632	
RCI	0.36, 0.658	
1-sided p-value	<.0001	
2-sided p-value	<.0001	

a Includes participants deemed lost to follow-up by the Investigator. b CIs derived via log–log transformation with back transformation to untransformed scale. c Brookmeyer–Crowley method. d Stratified by ECOG PS and geographic region by randomization. e Cox model; HR <1 favours EC+mFOLFOX6. f Repeated confidence interval method (EAST v6.5). g Log-rank test. Data cutoff: 06JAN2025.

Subgroup analysis according to choice of regimen in the control arm

OS was compared between the EC + mFOLFOX6 Arm and each regimen of the Control Arm administered in at least 10 participants. At the time of the PFS PCD, the HR for death estimated from Cox regression model stratified by ECOG PS and Geographic Region were:

- EC + mFOLFOX6 Arm vs mFOLFOX6 + bevacizumab regimen: 0.45 (95%CI: 0.323; 0.619)
- EC + mFOLFOX6 Arm vs FOLFOXIRI + bevacizumab regimen: 0.54 (95%CI: 0.357; 0.830)
- EC + mFOLFOX6 Arm vs CAPOX + bevacizumab regimen: 0.45 (95%CI: 0.290; 0.705)
- EC + mFOLFOX6 Arm vs mFOLFOX6 regimen: 0.41 (95%CI: 0.222, 0.746)

The treatment effect according to OS was consistently shown among subgroups regarding the choice of regimen in the control arm.

TTR by BICR assessment

The median TTR by BICR for responding participants in the EC + mFOLFOX6 Arm was 7.0 weeks (range: 5.1, 103.6) and in the Control Arm was 7.3 weeks (range: 5.4, 48.0).

PFS2 for EC + mFOLFOX6 vs Control

Median PFS2 was 20.7 months (95% CI: 19.0, 23.9) for participants in the EC + mFOLFOX6 Arm and 12.7 months (95% CI: 11.2, 13.7) for participants in the Control Arm.

Summary of PRO Results

EORTC QLQ-C30

At visits that included ≥10 participants eligible to complete the questionnaire (excluding EOT and follow-up visits), ≥92.3% of eligible participants in the EC + mFOLFOX6 Arm and ≥93.3% of eligible participants in the Control Arm completed all questions. Mean global QOL scores for the EC + mFOLFOX6 Arm and Control Arm were comparable from Screening to Week 72 suggesting that participant quality of life was maintained in both arms. After Week 72 the number of participants in the Control Arm decreased to fewer than 10 and became too small to allow meaningful comparisons to the EC + mFOLFOX6 Arm.

PGIS

At the Week 30 post-baseline visit, 140 eligible participants (97.2%) in the EC + mFOLFOX6 Arm and 89 eligible participants (97.8%) in the Control Arm completed all questions. Across all visits, no participants in either arm rated their symptoms as very severe. At baseline, participants in the EC + mFOLFOX6 Arm rated their symptoms as none (24.9%), mild (33.3%), moderate (27.9%), or severe (13.9%); and in the Control Arm rated their symptoms as none (26.4%), mild (35.2%), moderate (25.8%), or severe (12.6%). At the Week 30 post-baseline visit, participants in the EC + mFOLFOX6 Arm rated their symptoms as none (34.3%), mild (37.9%), moderate (21.4%), or severe (6.4%); and in the Control Arm rated their symptoms as none (38.2%), mild (39.3%), moderate (15.7%), or severe (6.7%).

PGIC

In the EC + mFOLFOX6 Arm and Control Arm, PGIC survey completion rates were generally high over all visits. Across all visits, no participants in either arm rated their change in symptoms as much better. At the Week 30 post-baseline visit, 140 eligible participants (97.2%) in the EC + mFOLFOX6 Arm and 89 eligible participants (97.8%) in the Control Arm completed all questions. At the Week 30 post-baseline visit, participants in the EC + mFOLFOX6 Arm rated their change in symptoms as a little better (38.6%), no change (38.6%), a little worse (18.6%), or much worse (4.3%); and participants in the Control Arm rated their change in symptoms as a little better (43.8%), no change (33.7%), a little worse (16.9%), or much worse (5.6%). At the end of treatment, participants in the EC + mFOLFOX6 Arm rated their change in symptoms as a little better (36.0%), no change (30.7%), a little worse (21.3%), or much worse (12.0%); and participants in the Control Arm rated their change in symptoms as a little better (25.0%), no change (33.0%), a little worse (22.7%), or much worse (19.3%).

Ancillary analyses

Comparison of EC arm vs control arm in study BREAKWATER

Enrollment into the encorafenib + cetuximab arm was terminated in amendment 5. Overall, 158 patients were enrolled to receive EC, 112 discontinued study treatment due to progressive disease and 91 have died. Twelve patients had ongoing treatment at PFS-DCO. Median age of patients was 59 years with mainly hepatic metastasised right sided tumours (56.3%). Other baseline characteristics were comparable. At the PFS DCO, ORR was 45.6% (95%CI: 38.0, 53.3) vs 65.7% (59.4, 71.4) vs 37.4% (31.6, 43.7) in the EC / EC+mFOLFOX6/ Control arm, respectively. Duration of response was 4.3 vs 9.2 vs 5.5 months. After a median follow-up of 18 months in the EC arm and 9.8 months for patients in the control arm, median PFS by BICR was 6.8 months (95% CI: 5.7, 8.3) vs 7.1 months (95% CI: 6.8, 8.5) for patients in the control arm, with a stratified HR for PFS by BICR of 1.09 (95% CI: 0.839, 1.422) in favour of the control arm. For the secondary endpoint OS, median OS was 19.5 months (95% CI: 17.6, 22.5) for patients in the EC arm and 15.1 months

(95% CI: 13.7, 17.7) for patients in the control arm, with a stratified HR for OS of 0.69 (95% CI: 0.529, 0.899) in favour of the EC arm.

Biomarker testing for patient selection

Scientific rationale and biomarker definition:

The BRAF V600E mutation occurs in approximately 8% to 12% of patients with mCRC. This point mutation in exon 15 results in a valine-to-glutamic acid change at codon 600 and confers a marked increase in kinase activity, estimated at approximately 500–700-fold above physiologic signaling levels leading to constitutive activation of BRAF kinase and sustained RAS/RAF/MEK/ERK pathway signaling, resulting in increased cell proliferation and survival (Piercey et al., 2024, see also page **Error! Bookmark not defined.**).

Analytical validation aspects of the therascreen BRAF V600E RGQ PCR Kit:

In the BREAKWATER clinical study, the therascreen BRAF V600E RGQ PCR Kit was the test used centrally to confirm BRAF V600E mutation. Analytical performances of the therascreen BRAF V600E RGQ PCR Kit are described below.

- Assay cutoff:

The cutoff was based on the difference between the Control reaction CT and the V600E Mutant reaction CT (ΔCT). Samples with ΔCT ≤7.0 were classified as "BRAF Mutation Detected", whereas samples with ΔCT >7.0 were classified as "No Mutation Detected".

- Limit of detection (LoD) / cut-point:

The measurable range of the therascreen BRAF V600E RGQ PCR Kit is defined by a Control reaction CT range of 20.95–33.00. The limit of detection (LoD) was established as the lowest mutation allelic fraction (MAF) detectable in 95% of replicates in a wild-type DNA background. Based on Probit analysis and verification studies using diluted FFPE CRC specimens, the overall LoD for the BRAF V600E assay was determined to be 7.8% MAF across all DNA input levels.

- Effect of DNA Input on Results:

Linearity studies across the assay's measurable range demonstrated that varying DNA input levels within the predefined Control Working Range did not significantly affect ΔCT values or assay interpretation. Minor quadratic or cubic effects observed were within assay precision limits.

- Interfering substances

Interference studies demonstrated that substances potentially remaining from the DNA extraction process, including paraffin wax, xylene, ethanol, and extraction buffers, did not affect assay results. In addition, haemoglobin concentrations up to 2 mg/ml did not interfere with mutation detection in either mutant or wild-type samples. The presence of 30–100% necrotic tissue in FFPE CRC samples also had no impact on assay amplification performance or result validity.

- Cross-reactivity (assay specificity):

Cross-reactivity testing showed no reactivity with BRAF V600K, V600R, V600M, or V600G mutations, whereas cross-reactivity was observed for V600Ec and V600D. The clinical impact of this cross-reactivity is considered minimal, as these mutations were not identified in the evaluated CRC clinical specimens.

- Precision:

- Repeatability

The precision of the therascreen BRAF V600E RGQ PCR Kit within-laboratory (repeatability) was assessed. Both correctness of mutation call results and the precision of ΔCT values (the difference in CT values between a Mutation Reaction and the Control Reaction) for positive test samples and Control CT values for negative test samples were measured.

Clinical CRC (primary and metastatic) FFPE samples representing different DNA input levels and different mutation percentage levels were used for this evaluation. The proportion of correct call in tumor resection is 100% in surgical resection and >96% in core needle biopsies.

- Reproducibility

The precision of the therascreen BRAF V600E RGQ PCR Kit between-laboratories (reproducibility) was assessed. Three different laboratories (test sites) were used. The same test panel was used for this study as for the repeatability study. The proportion of correct mutation calls and concordance of calls between kit lots for each sample was >98%.

- Sample handling variability

Sample handling variability was assessed for the therascreen BRAF V600E RGQ PCR Kit, specifically DNA extraction at multiple sites.

Sequential sections of 4–5 µm were cut from each of one CNB and eight FFPE RES samples, of which five were wild-type (including the CNB sample) and four were mutant (36 sections were cut per RES sample and 24 from the CNB CRC sample). In total, 156 extractions were performed and the rate of correct calls observed across all samples from all sites was 100% for the RES and CNB mutant samples, a rate of 97.22% correct calls was observed for the RES wild-type samples.

- Accuracy: comparison to the analytical reference method.

A concordance study using 600 FFPE samples demonstrated high agreement between the therascreen BRAF V600E RGQ PCR Kit and a validated bi-directional Sanger sequencing method, with an overall percent agreement of 95%. Comprehensive analytical validation confirmed robust assay performance for central BRAF V600E mutation testing in the C4221015 (BREAKWATER) trial.

Clinical validation:

Clinical validation of the CDx in the previous BEACON CRC trial

Concordance was shown based on in the BEACON CRC study in pretreated BRAF V600E mutated mCRC between the therascreen BRAF V600E RGQ PCR Kit and the Qiagen-developed real-time PCR BRAF V600E clinical trial assay (CTA) developed for enrolment on the study (see Table 30 and Table 31).

Table 30 Measures of agreement between CTA and CDx, BEACON study

Reference method	Measure of agreement	Frequencies	Percent agreement	Clopper-Pearson confidence limit %*	Clopper-Pearson confidence limit %*
None	OPA	679/680	99.85	99.18	100.00
CDx	PPA	263/264	99.62	97.91	99.99
CDx	NPA	416/416	100.00	99.12	100.00
CTA	PPA	263/263	100.00	98.61	100.00
CTA	NPA	416/417	99.76	98.67	99.99

OPA: Overall percent agreement; PPA: Positive percent agreement; NPA: Negative percent agreement; Clopper-Pearson (exact) binomial lower two-sided 95% confidence limit. Source: therascreen BRAF V600E RGQ PCR Kit Handbook, table 19

Table 31 Comparison of OS and ORR results using CTA or CDx, BEACON study

Endpoint	Assay	Doublet arm	Control arm	Treatment effect
Overall survival (OS)	CDx	Median OS: 8.4 months	Median OS: 5.2 months	Stratified HR 0.55 (95% CI: 0.406–0.744)
Overall survival (OS)	CTA	Median OS: 8.41 months	Median OS: 5.42 months	Stratified HR 0.60 (95% CI: 0.45–0.79)
Objective response rate (ORR)	CDx	17.6% (95% CI: 12.4–23.8)	1.1% (95% CI: 0.1–3.8)	N/A
Objective response rate (ORR)	CTA	20.4%	1.9%	N/A

Abbreviations: CDx = therascreen BRAF V600E RGQ PCR Kit; CTA = clinical trial assay; CI = confidence interval; HR = hazard ratio; OS = overall survival; ORR = objective response rate. N/A not applicable
Notes: CDx-based analyses were performed in randomised CDx-positive patients. CTA results correspond to the primary BEACON study analyses.

Clinical validation in the pivotal C4221015 (BREAKWATER) trial

Patients could be enrolled based on local PCR- or NGS-based detection of a BRAF V600E mutation in tumour tissue or blood, provided sufficient tumour tissue was available for mandatory central confirmation testing. Central confirmation using the therascreen BRAF V600E RGQ PCR Kit on tumour tissue obtained within 24 months was required within 30 days after treatment initiation. Among 479 randomised patients, 95.8% had centrally confirmed BRAF V600E-positive status, and sensitivity analyses were performed in the centrally confirmed biomarker-positive population (see Table 32).

Table 32 Summary of PFS Based on BICR Assessment (RECIST v1.1) Phase 3 EC+mFOLFOX6 vs Control – Central BRAF V600E Positive Analysis Set (Protocol C4221015)

Category	EC+mFOLFOX6 (N=228)	Control (N=231)
Participants with event, n (%)	118 (51.8)	128 (55.4)
Progressive disease	102 (44.7)	106 (45.9)
Death	16 (7.0)	22 (9.5)
Participants censored, n (%)	110 (48.2)	103 (44.6)
No adequate baseline assessment	4 (1.8)	2 (0.9)
Start of new anti-cancer therapy	50 (21.9)	63 (27.3)
Event after ≥2 missing post-baseline assessments	4 (1.8)	8 (3.5)
Withdrawal of consent	4 (1.8)	10 (4.4)
Lost to follow-up	1 (0.4)	1 (0.4)
No adequate post-baseline tumor assessment	0	0
Ongoing without an event	47 (20.6)	19 (8.2)
Probability of being event-free (95% CI) at 3 months	0.921 (0.875, 0.950)	0.831 (0.772, 0.876)
at 6 months	0.813 (0.752, 0.860)	0.612 (0.537, 0.678)
at 9 months	0.661 (0.589, 0.723)	0.410 (0.333, 0.486)
at 12 months	0.543 (0.469, 0.612)	0.301 (0.227, 0.378)
at 15 months	0.455 (0.381, 0.527)	0.208 (0.140, 0.285)
at 18 months	0.374 (0.299, 0.449)	0.197 (0.130, 0.274)
at 21 months	0.328 (0.251, 0.408)	0.179 (0.112, 0.258)
Kaplan–Meier Quartiles (95% CI)		
Q1	7.2 (6.2, 8.4)	4.3 (3.9, 5.3)
Median	13.6 (11.2, 16.4)	7.1 (6.8, 8.8)
Q3	32.9 (20.0, NE)	13.7 (11.1, 22.7)
Stratified analysis – Comparison vs Control		
Hazard Ratio	0.53	
95% CI	0.411, 0.689	
1-sided p-value	<.0001	
2-sided p-value	<.0001	

CIs derived using log–log transformation; Brookmeyer–Crowley for medians. Stratified by ECOG PS, region and randomization. Hazard ratio <1 favors EC+mFOLFOX6.

Cut point selection

No clinical cut-point was defined or evaluated.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of Efficacy for BREAKWATER study

Title: An Open-Label, Multicenter, Randomized Phase 3 Study of First-Line Encorafenib Plus Cetuximab With or Without Chemotherapy Versus Standard of Care Therapy With a Safety Lead-In of Encorafenib and Cetuximab Plus Chemotherapy in Participants With Metastatic BRAF V600E-Mutant Colorectal Cancer			
Study identifier	C4221015 US IND 115298 NCT04607421 EudraCT 2020-001288-99 EU CT 2023-509405-77-00 Also known as BREAKWATER study		
Design	BREAKWATER is an open-label, multicenter, 3-arm, randomized Phase 3 study of EC alone (EC Arm) or in combination with chemotherapy (mFOLFOX6; EC + mFOLFOX6 Arm) versus standard-of-care chemotherapies (mFOLFOX6, FOLFOXIRI, or CAPOX each with or without bevacizumab; Control Arm) in first-line participants with BRAF V600E-mutant mCRC.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months after the last participant enrolled (PFS Primary Completion Date) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	EC + mFOLFOX6 Arm		236 participants with BRAF V600E-mutant metastatic CRC were to receive encorafenib (300 mg QD) administered orally + cetuximab (500 mg/m^2 Q2W) + mFOLFOX6 both IV administered, in 28-day cycles until disease progression.
	Control Arm / SoC		243 participants with BRAF V600E-mutant metastatic CRC were to receive either: - mFOLFOX6, - or FOLFOXIRI in - or CAPOX in each with or without bevacizumab, in 28-day cycles until disease progression.
Endpoints and definitions	Primary endpoint	ORR by BICR	Objective Response Rate (ORR) as determined by Blinded Independent Central Review (BICR)
	Primary endpoint	PFS by BICR	Progression-Free Survival (PFS) defined as the time from the date of randomization to the earliest documented disease progression per RECIST v1.1, or death due to any cause

	Key secondary endpoint	OS	Overall Survival
	Secondary endpoint	ORR by investigator	Objective Response Rate (ORR) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	DOR by BICR	Duration of Response (DOR) as determined by Blinded Independent Central Review (BICR) per RECIST v1.1
	Secondary endpoint	DOR by investigator	Duration of Response (DOR) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	TTR by BICR	Time to Response (TTR) as determined by Blinded Independent Central Review (BICR) per RECIST v1.1
	Secondary endpoint	TTR by investigator	Time to Response (TTR) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	PFS by investigator	Progression-Free Survival (PFS) derived from Investigator assessment per RECIST v1.1
	Secondary endpoint	PFS2	PFS2, defined as the time from the date of randomization to the date of discontinuation of next-line treatment after first objective PD by Investigator assessment, the second objective disease progression, or death from any cause, whichever occurs first
Database lock	27 January 2025 (PFS Primary Analysis)		
Results and Analysis			
Analysis description	**ORR Primary Analysis (PCD 22 December 2023)**		
Analysis population and time point description	Full Analysis Set - ORR Subset, which included the first 110 participants randomized in each of the two arms, EC + mFOLFOX6 Arm and Control Arm. Imaging assessments were performed every 6 weeks from the date of randomization for the first 18 months of treatment, then every 8 weeks until BICR-confirmed disease progression, death, withdrawal of consent, lost of follow-up or final OS analysis.		
Descriptive statistics and estimate variability	Treatment group	EC + mFOLFOX6 Arm	Control Arm / SoC
	Number of subjects	110	110

	ORR per BICR (95% confidence interval [CI])	60.9% (51.6, 69.5)	40.0% (31.3, 49.3)
Effect estimate per comparison		Comparison groups	EC + mFOLFOX6 / Control
	ORR per BICR	Odds Ratio (Stratified)	2.443
		95% CI	(1.348, 4.380)
		1 sided p-value (Cochran-Mantel-Haenszel test)	0.0008
Analysis description	**PFS Primary Analysis (PCD 06 January 2025)**		
Analysis population and time point description	Full Analysis Set which included all participants randomized. DOR and TTR by BICR analyses were performed on responders only. DOR and TTR by investigator analyses were performed on responders only.		
Descriptive statistics and estimate variability	Treatment group	EC + mFOLFOX6 Arm	Control Arm / SoC
	Number of subjects	236	243
	PFS per BICR Median (95% CI)	12.8 months (11.2, 15.9)	7.1 months (6.8, 8.5)
	PFS by investigator Median (95% CI)	13.6 months (12.1, 16.1)	7.0 months (6.0, 8.3)
	OS Median (95% CI)	30.3 months (21.7 months, NE)	15.1 months (13.7 months, 17.7 months)
	ORR per BICR (95% CI)	65.7% (59.4, 71.4)	37.4% (31.6, 43.7)
	ORR by investigator (95% CI)	68.6% (62.5, 74.2)	40.7% (34.8, 47.0)
	DOR by BICR Median (95% CI)	13.9 months (10.9, 18.5)	10.8 months (7.6, 13.4)
	TTR by BICR (Range)	7.0 weeks (5.1, 103.6)	7.3 weeks (5.4, 48.0)
	DOR by investigator Median (95% CI)	12.5 months (10.9, 16.6)	8.3 months (6.6, 10.7)
	TTR by investigator (Range)	6.9 weeks (5.1, 103.0)	7.1 weeks (5.4, 42.3)
	PFS2 Median (95%CI)	20.7 months (19.0, 23.9)	12.7 months (11.2, 13.7)
Effect estimate per comparison		Comparison groups	EC + mFOLFOX6 / Control
		Stratified Hazard Ratio	0.53

	PFS per BICR	95% CI	0.407, 0.677
		1-sided p-value (log-rank test)	<.0001
	OS	Stratified HR	0.49
		95% CI	0.375, 0.632
		1-sided p-value (log-rank test)	<.0001
Notes	Primary analyses of ORR, PFS and OS were stratified by ECOG PS at baseline and Geographic Region. The primary analysis of PFS was based on a total of 254 PFS events (122 [51.7%] in the EC + mFOLFOX6 Arm and 132 [54.3%] in the Control Arm).		

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design

Study C4221015 (BREAKWATER) is an ongoing open-label, multiregional, randomized Phase III study evaluating encorafenib plus cetuximab in combination with mFOLFOX6 versus investigator's-choice oxaliplatin-based chemotherapy as first-line treatment for patients with BRAF V600E-mutant metastatic colorectal cancer (mCRC). The study employs dual primary endpoints (PFS by BICR and ORR by BICR), with OS designated as a key secondary endpoint.

CHMP Scientific Advice (July 2020) highlighted that allowing multiple chemotherapy backbones in the control arm could complicate interpretation of efficacy and safety. The omission of cetuximab from the SOC arm was specifically questioned. However, subsequent evidence further undermined the use of anti-EGFR therapy in BRAF V600E-mutant disease. Retrospective analyses and meta-analyses consistently demonstrated lack of benefit from anti-EGFR antibodies in this molecular subgroup, culminating in the 2023 ESMO Living Guideline stating that "the combination of anti-EGFR mAb with chemotherapy cannot be recommended in BRAF-mutant tumours." These data provided justification for excluding cetuximab from the reference therapy arm.

According to eligibility criteria, exclusion of MSI-H/dMMR –patients and those with RAS co-mutations is accepted. MSI-H/dMMR disease represents a biologically distinct subgroup with high sensitivity to immune-checkpoint inhibition and is therefore managed with alternative first-line therapeutic strategies. BRAF- and RAS alterations are considered to be mutually exclusive and to be non-overlapping molecular subsets (Clarke et al., 2015), with co-mutations reported only as rare isolated events (De Roock et al., 2010).

Patient enrolment was permitted based on local PCR- or NGS-based diagnostic testing demonstrating the presence of a BRAF V600E mutation in tumour tissue or blood (e.g. circulating tumour DNA). In addition, patients were required to provide enough representative tumour material to allow mandatory central confirmation of BRAF V600E mutation status using the therascreen BRAF V600E RGQ PCR Kit. No clinical cut-point was defined or evaluated. Of note, as the study has a targeted design (i.e. no patients without BRAF V600E mutation were included), the biomarker-by-treatment interaction to show that BRAF V600E mutation is predictive for a (larger) treatment effect cannot be investigated but assumes no (sufficient) treatment effect in the non-selected patients.

PFS by BICR was considered an acceptable primary endpoint, with OS expected to provide supportive evidence. Descriptive comparisons between Arm A (EC) and Arm B (EC+mFOLFOX6) were pre-specified and deemed appropriate, given the discontinuation of Arm A. The graphical gatekeeping procedure for multiplicity control and the stratification factors (geographic region and ECOG performance status) were considered adequate.

The justification for the selected combination regimen and the isolation of individual drug effects was only partially substantiated in the pivotal trial. The lack of efficacy of encorafenib monotherapy was inferred from preclinical models and early clinical studies. Introduction of the encorafenib–cetuximab doublet, despite the absence of an established role for cetuximab in BRAF V600E-mutated CRC when combined solely with chemotherapy, and omission of binimetinib—an established partner in melanoma and NSCLC—were supported primarily by evidence generated in the later-line BEACON CRC trial. Within the BREAKWATER study design, the EC doublet and the EC+mFOLFOX6 triplet were compared with standard of care to delineate the incremental contribution of chemotherapy.

Extended follow-up of the Safety Lead-in supported prioritisation of the combination regimens, as both EC+mFOLFOX6 and EC+FOLFIRI demonstrated acceptable tolerability and antitumour activity. Consequently, the Applicant introduced Cohort 3 comprising two randomized arms to evaluate EC+FOLFIRI versus FOLFIRI±bevacizumab in first-line BRAF V600E-mutant mCRC.

The target of estimation (estimand) for PFS in the primary analysis was the hypothetical effect if patients had not started new anticancer treatment. Accordingly, patients were censored at start of new anticancer treatment. A supplementary analysis was conducted in accordance with the EMA guideline for analysis of PFS (EMA/CHMP/27994/2008/Rev.1), where it is recommended to assign progression events regardless of violations, discontinuation of study drug or change of therapy.

For OS, all intercurrent events were accounted for by the treatment policy strategy.

Stratified randomisation was taken into account by a correspondingly stratified analysis.

The multiple testing strategy specified in the SAP ensures family-wise type 1 error control for the hypothesis tests for the dual primary endpoints PFS and OR, and the key secondary endpoint OS. The testing strategy would have allowed to declare study success if either of the dual primary endpoints OR or PFS had been met, however, dual primary endpoints OR and PFS are generally not recommended by CHMP and success based on OR alone would not have been accepted as basis for approval.

Conduct of clinical study

DCO for the ORR analysis was the 22nd Dec 2023, DCO for primary PFS analysis was 06th Jan 2025. Of note, the trial was amended relevantly while it was ongoing; in particular amendment 5 and 6 require attention.

Amendment 5 was implemented on 20th Dec 2022 after reaching FDA agreement in November 2022. Following this amendment

- enrolment into Arm A (EC) was discontinued due to low probability that EC alone would demonstrate superiority over SOC chemotherapy. This decision was informed by preliminary activity observed in the safety-lead in portion of the BREAKWATER study and supported by external data from the CEACON CRC trial and the ANCHOR-CRC trial.
- ORR was added as dual primary endpoint in the phase 3 portion of the BREAKWATER trial with the ORR analysis being planned to be conducted at the time the phase 3 portion is fully enrolled

or 8 months after randomisation of the first 110 participants in each arm (whichever occurs later).

Amendment 6 was implemented on 13th March 2024. Following this amendment, the required number of PFS events by BICR needed to conduct the primary PFS analysis for the phase 3 portion of the study was reduced from 331 events to at least 230 events (additionally requiring at least 12 months having passed after the completion of enrolment of the Phase 3 portion of the study) to enable a timely readout of the PFS due to a slower-than-expected accrual of events.

Such changes during an open-label confirmatory study are not in accordance with the usual standards. In particular, the reduction of required events for the primary PFS analysis can endanger the study integrity and may lead to inflation of type 1 error and bias. Furthermore, analysis of ORR (DCO 22nd Dec 2023) and application for accelerated approval at FDA on this basis may have influenced the ongoing study. The reduction of PFS events for primary PFS analysis in amendment 6 was performed just approximately 3 months after data cut-off for ORR analysis (13th March 2024). As to the respective FDA 'NDA/BLA Multi-disciplinary Review and Evaluation' on 24th April 2024 "the Applicant clarified that the trend of slower PFS events accumulation was observed prior to the ORR analysis and confirmed that the reduction in target PFS events was made prior to the ORR analysis". The MAH provided detailed and reassuring information on the firewalls and data access plan to prevent that data from the ongoing study were known to the study team. Particularly, it was clarified that protocol amendment 6, which was considered most critical for study integrity, was implemented before the database snapshot for Phase 3 ORR analysis where unblinded aggregated data were analysed. Although changes of critical design elements during an open-label study are not optimal, it is accepted that the firewalls were sufficient and changes were not driven by knowledge of data from the ongoing study. To support that the earlier data cut-off did not have a relevant impact on the conclusions from the study, an update of the PFS data was requested by CHMP but not possible as no follow-up for PFS events (according to clinical trial standards) was performed after final PFS analysis. However, sensitivity analyses supporting that conclusions on PFS would change only under unrealistic assumptions were provided. The conclusions of the PFS analysis can therefore be considered robust despite the protocol modifications. An update of the OS data will be provided as part of the close-out study report, currently expected in 2027 (post authorisation approval commitment-REC is agreed).

Efficacy data and additional analyses

The data presented are based on the PFS primary analysis data cut-off (06 January 2025). At this cut-off, 47 patients in the EC+mFOLFOX6 arm and 20 patients in the control arm were censored because they were ongoing without an event. A further 132 versus 77 patients were in survival follow-up. Deaths had occurred in 94 patients in the EC+mFOLFOX6 arm and 148 patients in the control arm, and 10 versus 18 patients had been lost to follow-up or had withdrawn consent.

Baseline characteristics were generally balanced across the EC+mFOLFOX6 and SOC arms. Median age was 60 vs 62 years; right-sided primary tumours occurred in 56.3% vs 61.9%; elevated baseline CEA in 70.8% vs 67.1%; liver metastases in 37.7% vs 34.2%; and median time from initial diagnosis was 6.81 vs 7.26 months in the EC vs SOC arm, respectively.

In the control arm (N=243), most participants received mFOLFOX6 + bevacizumab (39.9%), followed by FOLFOXIRI + bevacizumab (24.3%). Smaller proportions were treated with CAPOX + bevacizumab (16.9%), mFOLFOX6 without bevacizumab (7.4%), FOLFOXIRI (3.3%), or CAPOX (2.5%), representing a reliable distribution of treatment regimens.

Dose modifications were frequent. Encorafenib required dose reductions in 29.7% and dose interruptions in 72.8% of patients. Oxaliplatin—administered to all patients in both arms—showed higher rates of dose reductions (67.2% vs 54.6%) and dose interruptions (72.0% vs 51.1%) in the EC+mFOLFOX6 arm, consistent with greater cumulative toxicity.

The study met its dual primary endpoints, demonstrating a statistically significant and clinically meaningful improvement in PFS by BICR for EC+mFOLFOX6 compared with investigator's-choice chemotherapy ± bevacizumab. The stratified hazard ratio was 0.53 (95% CI: 0.407, 0.677). The Kaplan–Meier curves separate early and remain clearly divergent over time. Median PFS was 12.8 months (95% CI: 11.2, 15.9) for EC+mFOLFOX6 and 7.1 months (95% CI: 6.8, 8.5) for the control arm.

More than 20% of patients (EC+mFOLFOX6: 22.5%, investigator's-choice chemotherapy ± bevacizumab: 25.9%) were censored in the primary analysis because of start of new anti-cancer therapy. However, in accordance with protocol, patients were followed for progression irrespectively of the start of a new anti-cancer treatment and the PFS effect was supported by a supplementary analysis using a treatment policy strategy. The MAH clarified, that for start of a new anticancer therapy censored patients, 77.4% vs 88.9% in the treatment- vs control arm received systemic anticancer therapy, 18.9% vs 27.0% received at least one follow-up anticancer surgery. Despite an increased rate of censoring due to ≥2 missing or inadequate post-baseline assessments, this analysis provides consistent results and overall reassurance. Additional sensitivity analyses included RMST analyses, and unstratified regression analyses. PFS by investigator assessment, although secondary and non-primary, was directionally consistent with the BICR assessment. As expected, more progression events were reported by investigators (EC+mFOLFOX6: +11; control: +28), reflecting known differences in assessment frequency and stringency. The discrepancy rate between BICR and investigator PFS assessments was 20.8% in the EC+mFOLFOX6 arm and 13.2% in the control arm, which, although notable, does not undermine the primary BICR-based outcome.

From 479 randomised patients to the EC + mFOLFOX6 arm and the control arm, 95.8% had a positive confirmation of the presence of the BRAF V600E mutation based on the central tissue test therascreen BRAF V600E RGQ PCR Kit. Efficacy results were similar in this subgroup compared to the FAS result (HR 0.53; 95% CI 0.411, 0.689).

No clinical cut-point for biomarker positivity was defined or evaluated for the applied biomarker testing (BRAF V600E mutation). Therefore, it is unclear whether using a different positivity threshold would improve the benefit–risk balance.

The second primary endpoint, ORR by BICR, was met at the ORR data cut-off. In the descriptive analysis at the PFS cut-off, confirmed ORR was 65.7% (95% CI: 59.4, 71.4) in the EC+mFOLFOX6 arm and 37.4% (95% CI: 31.6, 43.7) in the control arm, DOR was 13.9 months (10.9, 18.5) vs 10.8 months (7.6, 13.4) in patients who responded.

Overall survival, the key secondary endpoint, was clearly positive. Median OS was 30.3 months (95% CI: 21.7, NE) in the EC+mFOLFOX6 arm versus 15.1 months (95% CI: 13.7, 17.7) in the control arm. The hazard ratio for death was 0.49 (95% CI: 0.375, 0.632; RCI 0.36, 0.658; one-sided $p<0.0001$). This represents a clinically meaningful and robust survival benefit. Supportive sensitivity analyses, low loss-to-follow-up rates, and the distribution of subsequent anticancer therapy strengthen the reliability of the observed effect. Notably, 57.2% of control-arm patients received post-protocol therapy, including 41.2% who received a BRAF inhibitor and more patients received surgery in the control arm, which would be expected to diminish the OS treatment difference rather than inflate it.

Sensitivity analyses by control regimen demonstrated consistent treatment effects across subgroups for both primary and secondary endpoints. While FOLFOXIRI plus bevacizumab showed a relatively more favourable PFS by BICR compared with other control regimens—albeit still inferior to the experimental arm—this relative advantage was no longer observed for OS.

The effect found in the primary endpoints and key secondary endpoint is supported by findings of PFS2 with a median PFS2 of 20.7 months (95% CI: 19.0, 23.9) for participants in the EC + mFOLFOX6 Arm and 12.7 months (95% CI: 11.2, 13.7) in the control arm.

In contrast to the EC+mFOLFOX6 regimen, the EC arm demonstrated a substantially lower response rate, supporting an incremental contribution of concomitant chemotherapy to antitumour activity. Relative to the control arm, median PFS in the 158 patients treated with EC was shorter and associated with a numerically unfavourable hazard ratio (HR 1.09; 95% CI 0.839, 1.422). Notably, both PFS2 and OS were numerically longer in the EC arm than in the control arm, which may reflect preserved sensitivity to subsequent chemotherapy.

FOLFOX is used in the SmPC instead of mFOLFOX6 in order to allow flexibility for minor clinical modifications of the FOLFOX regimen and to align with other regulatory decisions.

2.6.4. Conclusions on the clinical efficacy

The single pivotal study demonstrated a clinically meaningful efficacy advantage of encorafenib plus cetuximab with mFOLFOX6 over standard chemotherapy in first-line BRAF V600E-mutant mCRC. Both primary endpoints were met, with a robust improvement in PFS supported by consistent sensitivity analyses, alongside higher response rates. The substantial overall survival benefit further supports the robustness and clinical relevance of the treatment effect.

2.7. Clinical safety

Introduction

The safety data is mainly based on parts of study C4221015 (BREAKWATER study):

- Cohort 2 - EC in combination with mFOLFOX6 from the Safety lead in (SLI) portion of BREAKWATER up to the data cutoff date of 22 December 2023 (N=27). The SLI was conducted in patients with BRAF V600E-mutant mCRC with 0-1 prior systemic therapy regimen in the metastatic setting
- Randomized Phase 3 portion of the BREAKWATER study, which is described to summarize the safety of the combination of encorafenib + cetuximab with mFOLFOX6 and of a Control arm (including standard of care therapies) in patients with previously untreated BRAF V600E-mutant mCRC, up to the data cutoff date of 06 January 2025 (N=232 for the EC + m FOLFOX6 arm and N = 229 for the Control arm)

Safety assessments performed in BREAKWATER included collection of all AEs (serious and nonserious), laboratory test evaluations (haematology/coagulation, clinical chemistry, urinalysis, and pregnancy tests), physical examinations, dermatologic examinations, 12-lead ECGs, recording of vital signs, and verification of concomitant treatments.

As of the data cutoff date (06 Jan 2025), the enrolment in the Phase 3 was completed with 637 participants randomized (158 EC arm, 236 EC + mFOLFOX6 arm, and 243 Control arm). Of the participants randomized, 614 participants (153 EC Arm, 232 EC + mFOLFOX6 arm, 229 Control arm) received at least a dose of study treatment and were included in the Safety Analysis Set.

Patient exposure

Patient exposure

In the Phase 3 portion of BREAKWATER, a total of 232 participants were exposed to the combination of encorafenib 300mg QD with cetuximab 500 mg/m2 Q2W and mFOLFOX6. In the control arm (229 participants), all participants received oxaliplatin, with 71% of participants receiving a 5-FU+oxaliplatin based chemotherapy regimen (47.3% FOLFOX and 23.7% FOLFOXIRI), and the remaining participants received CAPOX. More than eighty percent (81.1 %) participants received bevacizumab in the control arm. As of the PCD for the PFS, the median duration of exposure to EC + mFOLFOX6 was close to twice longer than in the Control arm:

- The median duration of exposure to study treatment was 11.45 months (i.e 49.8 weeks, range: 1.3 to 161.9 weeks) in the EC + mFOLFOX6 arm (N=232) and 5.95 months (i.e 25.9 weeks range: 2.0 to 150.0 weeks) in the Control arm (N=229), with 28.4%, and 6.6% of participants respectively, still receiving study treatment at the time of the data cutoff.
- Of note, the median duration of exposure to oxaliplatin was shorter compared to that of the overall study treatment regimen in the EC + mFOLFOX6 arm (21.3 weeks [range: 1.3 to 141.1 weeks] vs 49.8 weeks [range: 1.3 to 161.9 weeks], respectively) and in the Control arm (19.0 weeks [range: 2.0 to 98.3 weeks] vs 25.9 weeks [range: 2.0 to 150.0 weeks], respectively).

Table 34: Duration of Exposure by Study Treatment in BREAKWATER – (Safety Set)

	Phase 3 and SLI (Pooled)	SLI	Phase 3 portion	
	EC-FOLFOX-P (N=259)	EC+ mFOLFOX6 (N=27)	EC+ mFOLFOX6 (N=232)	Control (N=229)
Duration of Exposure (months)				
n	259	27	153	232	229
Mean (SD)	12.74 (8.433)	12.61 (10.785)	9.13 (7.881)	12.75 (8.144)	7.10 (5.711)
Q1/Median/Q3	5.75 / 11.27 / 18.37	4.83 / 8.71 / 21.06	4.40 / 6.21 / 11.01	6.00 / 11.45 / 18.28	3.02 / 5.95 / 8.97
Min; Max	0.30; 37.22	0.92; 33.45	0.46; 35.32	0.30; 37.22	0.46; 34.50

A high median relative dose intensity was achieved for most study intervention components in the EC + mFOLFOX6 arm:

- Encorafenib: 89.9% (range: 3.0% to 100.0%),
- Cetuximab: 92.6% (range: 38.4% to 117.3%),
- 5-Fluorouracil: 80.0% (range: 49.9% to 102.5%),
- leucovorin: 92.5% (range: 48.3% to 166.9%),
- oxaliplatin: 82.6% (range: 30.5% to 201.9%).

EC + mFOLFOX6 SLI cohort

Similarly in the EC + mFOLFOX6 cohort of the SLI portion, a high median relative dose intensity was achieved for most study intervention components

Demographic and baseline characteristics

Regarding the demographic and baseline characteristics please be referred to the efficacy part of the AR.

Adverse events

Table S02 provides an overview of AEs by treatment arms for the BREAKWATER Phase 3 portion, SLI portion and the pooled EC-FOLFOX-P population in comparison with the control arm.

Table 35: Overview of Adverse Events-Overall and Maximum Grade ≥3, Grade 3, Grade 4 and Grade 5

	Phase 3 and SLI (Pooled)	**SLI**	**Phase 3**	
	EC-FOLFOX-P (N=259) n(%)	**EC+ mFOLFOX6 (N=27) n(%)**	**EC+ mFOLFOX6 (N=232) n(%)**	**Control (N=229) n(%)**
Patients with at least 1 TEAE regardless of causality	259 (100.0)	27 (100.0)	232 (100.0)	227 (99.1)
Grade 3+	219 (84.6)	20 (74.1)	199 (85.8)	163 (71.2)
Grade 3	154 (59.5)	14 (51.9)	140 (60.3)	125 (54.6)
Grade 4	53 (20.5)	4 (14.8)	49 (21.1)	28 (12.2)
Grade 5	12 (4.6)	2 (7.4)	10 (4.3)	10 (4.4)
Drug related	259 (100.0)	27 (100.0)	232 (100.0)	217 (94.8)
Grade 3+	196 (75.7)	19 (70.4)	177 (76.3)	135 (59.0)
Grade 3	151 (58.3)	14 (51.9)	137 (59.1)	111 (48.5)
Grade 4	45 (17.4)	5 (18.5)	40 (17.2)	23 (10.0)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Patients with at least 1 SAE regardless of causality	119 (45.9)	12 (44.4)	107 (46.1)	89 (38.9)
Grade 3+	106 (40.9)	11 (40.7)	95 (40.9)	74 (32.3)
Grade 3	75 (29.0)	8 (29.6)	67 (28.9)	53 (23.1)
Grade 4	19 (7.3)	1 (3.7)	18 (7.8)	11 (4.8)
Grade 5	12 (4.6)	2 (7.4)	10 (4.3)	10 (4.4)
SAE drug related	52 (20.1)	7 (25.9)	45 (19.4)	50 (21.8)
Grade 3+	41 (15.8)	5 (18.5)	36 (15.5)	44 (19.2)
Grade 3	33 (12.7)	4 (14.8)	29 (12.5)	33 (14.4)
Grade 4	8 (3.1)	1 (3.7)	7 (3.0)	10 (4.4)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
TEAE leading to discontinuation of all study treatment*	19 (7.3)	3 (11.1)	16 (6.9)	39 (17.0)
Grade 3+	16 (6.2)	2 (7.4)	14 (6.0)	35 (15.3)
Grade 3	9 (3.5)	0 (0.0)	9 (3.9)	23 (10.0)
Grade 4	2 (0.8)	1 (3.7)	1 (0.4)	7 (3.1)
Grade 5	5 (1.9)	1 (3.7)	4 (1.7)	5 (2.2)
TEAE leading to discontinuation of any study treatment*	69 (26.6)	8 (29.6)	61 (26.3)	39 (17.0)
Grade 3+	41 (15.8)	6 (22.2)	35 (15.1)	35 (15.3)
Grade 3	32 (12.4)	3 (11.1)	29 (12.5)	23 (10.0)
Grade 4	4 (1.5)	2 (7.4)	2 (0.9)	7 (3.1)
Grade 5	5 (1.9)	1 (3.7)	4 (1.7)	5 (2.2)

	Phase 3 and SLI (Pooled)	SLI	Phase 3	
	EC-FOLFOX-P (N=259) n(%)	EC+ mFOLFOX6 (N=27) n(%)	EC+ mFOLFOX6 (N=232) n(%)	Control (N=229) n(%)
TEAE requiring dose reduction of any study drug	171 (66.0)	19 (70.4)	152 (65.5)	124 (54.1)
Grade 3+	72 (27.8)	12 (44.4)	60 (25.9)	48 (21.0)
Grade 3	59 (22.8)	10 (37.0)	49 (21.1)	37 (16.2)
Grade 4	13 (5.0)	2 (7.4)	11 (4.7)	11 (4.8)
TEAE requiring dose interruption of any study drug	238 (91.9)	26 (96.3)	212 (91.4)	168 (73.4)
Grade 3+	180 (69.5)	15 (55.6)	165 (71.1)	87 (38.0)
Grade 3	146 (56.4)	11 (40.7)	135 (58.2)	79 (34.5)
Grade 4	34 (13.1)	4 (14.8)	30 (12.9)	8 (3.5)
TEAE requiring additional therapy	251 (96.9)	26 (96.3)	225 (97.0)	212 (92.6)
Grade 3+	160 (61.8)	15 (55.6)	145 (62.5)	114 (49.8)
Grade 3	130 (50.2)	14 (51.9)	116 (50.0)	86 (37.6)
Grade 4	30 (11.6)	1 (3.7)	29 (12.5)	27 (11.8)

Common Adverse events (AEs)

Table 36 provides the most frequently reported all causality AEs by SOC (incidence ≥50%) for the safety set of the BREAKWATER Study.

Table 36: Treatment Emergent Adverse Events by System Organ Class (≥50% in any treatment arm)– Overall and Maximum Grade ≥3, Grade 3, Grade 4 and Grade 5 [Safety Set]

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
	Grade	EC-FOLFOX-P (N= 259) n(%)	EC+ mFOLFOX6 (N= 27) n(%)	EC+ mFOLFOX6 (N= 232) n(%)	Control (N= 229) n(%)
Any Treatment Emergent Adverse Events	All Grades	259 (100.0)	27 (100.0)	232 (100.0)	227 (99.1)
	Grade 3+	219 (84.6)	20 (74.1)	199 (85.8)	163 (71.2)
Gastrointestinal disorders	All Grades	229 (88.4)	27 (100.0)	202 (87.1)	196 (85.6)
	Grade 3+	60 (23.2)	7 (25.9)	53 (22.8)	46 (20.1)
Nervous system disorders	All Grades	213 (82.2)	22 (81.5)	191 (82.3)	165 (72.1)
	Grade 3+	67 (25.9)	6 (22.2)	61 (26.3)	27 (11.8)

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
	Grade	EC-FOLFOX-P (N= 259) n(%)	EC+ mFOLFOX6 (N= 27) n(%)	EC+ mFOLFOX6 (N= 232) n(%)	Control (N= 229) n(%)
Skin and subcutaneous tissue disorders	All Grades	206 (79.5)	18 (66.7)	188 (81.0)	79 (34.5)
	Grade 3+	18 (6.9)	2 (7.4)	16 (6.9)	2 (0.9)
General disorders and administration site conditions	All Grades	210 (81.1)	23 (85.2)	187 (80.6)	148 (64.6)
	Grade 3+	37 (14.3)	1 (3.7)	36 (15.5)	20 (8.7)
Investigations	All Grades	180 (69.5)	16 (59.3)	164 (70.7)	138 (60.3)
	Grade 3+	101 (39.0)	13 (48.1)	88 (37.9)	65 (28.4)
Blood and lymphatic system disorders	All Grades	160 (61.8)	15 (55.6)	145 (62.5)	113 (49.3)
	Grade 3+	72 (27.8)	5 (18.5)	67 (28.9)	43 (18.8)
Metabolism and nutrition disorders	All Grades	160 (61.8)	16 (59.3)	144 (62.1)	99 (43.2)
	Grade 3+	26 (10.0)	3 (11.1)	23 (9.9)	14 (6.1)
Musculoskeletal and connective tissue disorders	All Grades	147 (56.8)	14 (51.9)	133 (57.3)	50 (21.8)
	Grade 3+	9 (3.5)	0	9 (3.9)	5 (2.2)
Infections and infestations	All Grades	139 (53.7)	16 (59.3)	123 (53.0)	98 (42.8)
	Grade 3+	33 (12.7)	4 (14.8)	29 (12.5)	20 (8.7)

Table 37 provides a summary of overall and Grade ≥3 treatment-related events reported in at least 10% of participants of the safety set.

Table 37: Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term for any Preferred Term≥10% in any population– Overall and Maximum Grade ≥ 3 [Safety Set]

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	Grades	EC-FOLFOX-P (N= 259) n(%)	EC+ mFOLFOX6 (N= 27) n(%)	EC+ mFOLFOX6 (N= 232) n(%)	Control (N= 229) n(%)
Number of subjects with related TEAE	All Grades	259 (100.0)	27 (100.0)	232 (100.0)	217 (94.8)
	Grade 3+	196 (75.7)	19 (70.4)	177 (76.3)	135 (59.0)
Nervous system disorders					
Neuropathy peripheral	All Grades	67 (25.9)	5 (18.5)	62 (26.7)	53 (23.1)
	Grade 3+	17 (6.6)	0	17 (7.3)	8 (3.5)

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	**Grades**	**EC-FOLFOX-P (N= 259) n(%)**	**EC+ mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
Peripheral sensory neuropathy	All Grades	71 (27.4)	9 (33.3)	62 (26.7)	54 (23.6)
	Grade 3+	17 (6.6)	1 (3.7)	16 (6.9)	8 (3.5)
Dysgeusia	All Grades	38 (14.7)	4 (14.8)	34 (14.7)	30 (13.1)
	Grade 3+	0	0	0	0
Paraesthesia	All Grades	34 (13.1)	2 (7.4)	32 (13.8)	19 (8.3)
	Grade 3+	12 (4.6)	2 (7.4)	10 (4.3)	4 (1.7)
Neurotoxicity	All Grades	32 (12.4)	6 (22.2)	26 (11.2)	19 (8.3)
	Grade 3+	14 (5.4)	1 (3.7)	13 (5.6)	0
Skin and subcutaneous tissue disorders					
Rash	All Grades	71 (27.4)	7 (25.9)	64 (27.6)	5 (2.2)
	Grade 3+	3 (1.2)	0	3 (1.3)	0
Alopecia	All Grades	55 (21.2)	2 (7.4)	53 (22.8)	26 (11.4)
	Grade 3+	0	0	0	0
Dermatitis acneiform	All Grades	50 (19.3)	7 (25.9)	43 (18.5)	1 (0.4)
	Grade 3+	2 (0.8)	0	2 (0.9)	0
Skin hyperpigmentation	All Grades	44 (17.0)	2 (7.4)	42 (18.1)	7 (3.1)
	Grade 3+	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	All Grades	40 (15.4)	4 (14.8)	36 (15.5)	22 (9.6)
	Grade 3+	7 (2.7)	0	7 (3.0)	2 (0.9)
Dry skin	All Grades	38 (14.7)	4 (14.8)	34 (14.7)	9 (3.9)
	Grade 3+	1 (0.4)	0	1 (0.4)	0
Pruritus	All Grades	30 (11.6)	3 (11.0)	27 (11.6)	4 (1.7)
	Grade 3+	0	0	0	0
Gastrointestinal disorders					
Nausea	All Grades	135 (52.1)	19 (70.4)	116 (50.0)	107 (46.7)
	Grade 3+	7 (2.7)	0	7 (3.0)	8 (3.5)

System Organ Class Preferred Term	Grades	Phase 3 and SLI (Pooled) EC-FOLFOX-P (N= 259) n(%)	SLI EC+ mFOLFOX6 (N= 27) n(%)	Phase 3 EC+ mFOLFOX6 (N= 232) n(%)	 Control (N= 229) n(%)
Vomiting	All Grades	83 (32.0)	6 (22.2)	77 (33.2)	44 (19.2)
	Grade 3+	7 (2.7)	1 (3.7)	6 (2.6)	4 (1.7)
Diarrhoea	All Grades	73 (28.2)	9 (33.3)	64 (27.6)	105 (45.9)
	Grade 3+	4 (1.5)	2 (7.4)	2 (0.9)	10 (4.4)
Stomatitis	All Grades	40 (15.4)	6 (22.2)	34 (14.7)	33 (14.4)
	Grade 3+	5 (1.9)	0	5 (2.2)	3 (1.3)
Constipation	All Grades	27 (10.4)	2 (7.4)	25 (10.8)	23 (10.0)
	Grade 3+	0	0	0	1 (0.4)
General disorders and administration site conditions					
Fatigue	All Grades	63 (24.3)	7 (25.9)	56 (24.1)	57 (24.9)
	Grade 3+	3 (1.2)	0	3 (1.3)	5 (2.2)
Asthenia	All Grades	62 (23.9)	7 (25.9)	55 (23.7)	31 (13.5)
	Grade 3+	8 (3.1)	0	8 (3.4)	3 (1.3)
Mucosal inflammation	All Grades	34 (13.1)	1 (3.7)	33 (14.2)	23 (10.0)
	Grade 3+	4 (1.5)	0	4 (1.7)	1 (0.4)
Pyrexia	All Grades	30 (11.6)	5 (18.5)	25 (10.8)	11 (4.8)
	Grade 3+	4 (1.5)	1 (3.7)	3 (1.3)	0
Investigations					
Neutrophil count decreased	All Grades	84 (32.4)	7 (25.9)	77 (33.2)	67 (29.3)
	Grade 3+	50 (19.3)	6 (22.2)	44 (19.0)	39 (17.0)
Platelet count decreased	All Grades	57 (22.0)	5 (18.5)	52 (22.4)	31 (13.5)
	Grade 3+	3 (1.2)	0	3 (1.3)	3 (1.3)
White blood cell count decreased	All Grades	42 (16.2)	0	42 (18.1)	31 (13.5)
	Grade 3+	13 (5.0)	0	13 (5.6)	8 (3.5)
Lipase increased	All Grades	45 (17.4)	4 (14.8)	41 (17.7)	13 (5.7)
	Grade 3+	36 (13.9)	4 (14.8)	32 (13.8)	6 (2.6)

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	**Grades**	**EC-FOLFOX-P (N= 259) n(%)**	**EC+ mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
Weight decreased	All Grades	36 (13.9)	1 (3.7)	35 (15.1)	14 (6.1)
	Grade 3+	3 (1.2)	0	3 (1.3)	0
Alanine aminotransferase increased	All Grades	27 (10.4)	1 (3.7)	26 (11.2)	24 (10.5)
	Grade 3+	3 (1.2)	0	3 (1.3)	4 (1.7)
Aspartate aminotransferase increased	All Grades	22 (8.5)	1 (3.7)	21 (9.1)	25 (10.9)
	Grade 3+	2 (0.8)	0	2 (0.9)	3 (1.3)
Blood and lymphatic system disorders					
Anaemia	All Grades	83 (32.0)	5 (18.5)	78 (33.6)	45 (19.7)
	Grade 3+	25 (9.7)	2 (7.4)	23 (9.9)	6 (2.6)
Neutropenia	All Grades	62 (23.9)	7 (25.9)	55 (23.7)	56 (24.5)
	Grade 3+	38 (14.7)	3 (11.1)	35 (15.1)	23 (10.0)
Thrombocytopenia	All Grades	36 (13.9)	5 (18.5)	31 (13.4)	19 (8.3)
	Grade 3+	0	0	0	0
Metabolism and nutrition disorders					
Decreased appetite	All Grades	81 (31.3)	6 (22.2)	75 (32.3)	47 (20.5)
	Grade 3+	3 (1.2)	0	3 (1.3)	2 (0.9)
Hypomagnesaemia	All Grades	40 (15.4)	6 (22.2)	34 (14.7)	5 (2.2)
	Grade 3+	4 (1.5)	1(3.7)	3 (1.3)	1 (0.4)
Musculoskeletal and connective tissue disorders					
Arthralgia	All Grades	52 (20.1)	5 (18.5)	47 (20.3)	0
	Grade 3+	4 (1.5)	0	4 (1.7)	0
Myalgia	All Grades	30 (11.6)	2 (7.4)	28 (12.1)	6 (2.6)
	Grade 3+	0	0	0	0
Respiratory, thoracic and mediastinal disorders					
Epistaxis	All Grades	33 (12.7)	5 (18.5)	28 (12.1)	28 (12.2)
	Grade 3+	0	0	0	0

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	**Grades**	**EC-FOLFOX-P (N= 259) n(%)**	**EC+ mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Melanocytic naevus	All Grades	13 (5.0)	2 (7.4)	11 (4.7)	0
	Grade 3+	1 (0.4)	0	1 (0.4)	0
Vascular disorders					
Hypertension	All Grades	3 (1.2)	3 (2.0)	3 (1.3)	30 (13.1)
	Grade 3+	0	1 (0.7)	0	5 (2.2)

Adverse events by severity

Overall, 85.8% of participants in the EC + mFOLFOX6 arm experienced at least one Grade ≥3 event (60.3% with a maximum Grade 3, 21.1% Grade 4 and 4.3% Grade 5).

Neutrophil count decreased (19.0%), lipase increase (17.2%), anaemia and neutropenia 15.1% (each), neuropathy peripheral (7.8%), peripheral sensory neuropathy (6.9%), neurotoxicity and white blood cell decreased (5.6% each) and asthenia (5.2%) were the most commonly (≥5% incidence) reported Grade≥ 3AEs in the EC + mFOLFOX6 arm, and in the Control arm were neutrophil count decreased (17.0%), neutropenia (10.0%), and lipase increased (6.1%).

Grade 3 or 4 AEs were reported more frequently in the EC + mFOLFOX6 arm as compared to the Control arm (81.5% vs 67.8%); the comparison between the EC + mFOLFOX6 and Control arms showed that Grade ≥ 3 lipase increased (17.2% vs 6.1%), anaemia (15.1% vs 3.9%) neutropenia (15.1% vs 10.0%) and neurotoxicity (5.6% vs none) were reported more frequently (≥5% difference) in the EC + mFOLFOX6 arm.

No Grade ≥3 AEs were more frequently reported (≥5% difference in incidence) in the Control arm than the EC + mFOLFOX6 arm.

Of note, in the EC + mFOLFOX6 arm, the notable frequency of Grade ≥ 3 AEs of lipase increased (17.2%) was not associated with an increased frequency of pancreatitis (pancreatitis or pancreatitis acute was <1%). Despite Grade ≥ 3 neutrophil count decreased being 19.0%, the reported frequency of febrile neutropenia was 2.2%.

Incidence of Adverse events over study treatment

In both the EC+ mFOLFOX6 and the control arms the majority of participants experienced their first adverse events during the first month of treatment (95.7% and 92.1% respectively). The adverse events (AEs) that occurred most frequently during the first month of treatment, with more than 50% of participants experiencing a first onset during this period in the EC+mFOLFOX6 arm, included pigmentation disorder (82.4%), nausea (74.4 %), white blood cell count decreased (68.1%), neutrophil count decreased (67.1%), headache (65.7%), ALT increased (65.5%) decreased appetite (63.2%), neurotoxicity (61.5%), malaise (60.0%) mucosal inflammation(55.9%), asthenia (50.0%) and fatigue (63.2%), vomiting (61.9%), neutropenia (57.1%), weight decreased (50.0%).

The AEs that occurred most frequently after 3 months of treatment, with more than 30% of participants experiencing a first onset during this period, included neurological events (neuropathy peripheral: 45.3% vs 20.5% in the control arm where they occurred more frequently in the first month) and musculoskeletal events (arthralgia (63%) and myalgia (55.3%), whereas in the control arm they were usually reported in the first month) as well as anaemia (54.9%) and thrombocytopenia (65.6%).

Adverse drug reactions in the target indication

Known ADRs of encorafenib in combination with cetuximab (EC), as evaluated in the MAA for the treatment of adult patients with BRAF V600E mutant mCRC who have received prior systemic treatment are reflected in the current Braftovi SmPC Section 4.8.

The existing list of ADRs from EC as determined for the MAA in previously treated mCRC population and defined based on the safety data of BEACON CRC served as the background for the determination of ADRs for the current application. For completeness, a clinical review was conducted on the final data from BEACON CRC up to the last patient last visit date of 10 November 2022 at a data snapshot of 06 December 2022 to identify any new PT as compared to the data cutoff of 15 August 2019. No new PT or safety signal emerged from this review.

The determination of the ADRs for encorafenib given in combination with cetuximab and FOLFOX is based on the safety data from the BREAKWATER study.

A clinical review of the safety data from the BREAKWATER EC-FOLFOX-P population was conducted. For the identification of potential ADRs, the following strategy was used:

- AEs that occurred in the BREAKWATER study at a greater incidence (≥5% difference) in the EC + mFOLFOX6 arm and / or EC-FOLFOX-P compared to the Control arm, and in the EC + mFOLFOX6 arm and/or EC-FOLFOX-P compared to the BREAKWATER EC arm were considered for review and addition to the list of potential ADRs of EC + FOLFOX.
- Events that occurred in the EC + mFOLFOX6 arm and / or in EC-FOLFOX-P at frequencies similar to these observed for the ADRs of oxaliplatin, leucovorin or 5-FU as listed in their PI labels were also considered for review and addition to the list of potential ADRs of EC + FOLFOX.

The addition of FOLFOX to the combination of encorafenib and cetuximab led to an increased incidence of several adverse reactions, commonly reported with oxaliplatin/5-fluorouracil containing regimen notably weight loss, stomatitis/mucositis, anaemia, neutropenia, leukopenia, and thrombocytopenia.

The most common ADRs (≥25%) of EC + FOLFOX as determined in the EC-FOLFOX-P population of BREAKWATER were:

Neuropathy peripheral (76.4%), neutropenia (56.4%), nausea (56.0%), fatigue (54.1%), anaemia (43.6%), diarrhoea (41.3%), vomiting and decreased appetite (36.7% each), rash (35.9%), thrombocytopenia (35.1%), abdominal pain and haemorrhage (32.8% each), arthralgia (32.4%) and pyrexia (31.7%), constipation (27.0%) mucosal inflammation (26.3%) and infection (25.5%).

Several new ADRs were reported for EC+FOLFOX:

Neutropenia, leukopenia, , thrombocytopenia, mucosal inflammation, hypoalbuminaemia, weight decreased and infection, and the common ADRs of hypokalaemia, hypomagnesaemia, upper respiratory tract infection, and sepsis.

ADRs with a change in frequency category were as follows:

Change to a higher frequency category:

- From common with EC to very common with EC +FOLFOX: drug hypersensitivity (1.9% to 10.8%), dysgeusia (4.6% to 17.8%), skin hyperpigmentation (7.4% to 17.8%), palmar-plantar erythrodysaesthesia syndrome (5.1% to 15.8%), alopecia (4.2% to 21.2%), transaminases increased (8.8% to 17.0%),
- From uncommon to very common: lipase increased (0.5% to 23.6%),
- From uncommon to common: basal cell carcinoma (0.5% to 1.2%), skin exfoliation (0.5% to 1.2%), amylase increased (0.5% to 2.7%)

Change to a lower frequency category:

- From very common with EC to common with EC +FOLFOX: melanocytic naevus (15.7% to 5.8%), pain in extremity (11.6% to 9.7%),
- From common to uncommon: new primary melanoma (1.9% to 0.8%)

ADRs of EC + FOLFOX reported with increased incidence (≥10% difference, with or without change in frequency category) as compared to the known incidence of EC ADRs are:

- The very common EC ADRs of neuropathy peripheral, haemorrhage, nausea and pyrexia (these events remain very common),
- The common EC ADRs of drug hypersensitivity, dysgeusia, skin hyperpigmentation, palmar-plantar erythrodysaesthesia syndrome and alopecia that become very common
- The uncommon EC ADR of lipase increased that becomes very common.

ADRs of EC + FOLFOX reported with decreased incidence (≥10% difference, with or without change in frequency category) as compared to the known incidence of EC ADRs are

- The very common EC ADRs of melanocytic naevus that becomes common and acneiform dermatitis that remains very common.

Section 4.8 of the SmPC was adapted accordingly. Table 5 in section 4.8 has been expanded to include a new column, and the descriptions of selected adverse reactions have been updated to include relevant new information.

Table 38 Tabulated list of ADRs with encorafenib 300 mg in combination with cetuximab and FOLFOX in support of the amendments in section 4.8 of the SmPC

Frequency	Encorafenib 300 mg in combination with cetuximab and FOLFOX (n = 259)
Neoplasms benign, malignant and unspecified	
Common	Melanocytic naevus (n=15) Skin papilloma* (n=8) Basal cell carcinoma (n=3) cuSCC[a] (n=3)
Uncommon	New Primary Melanoma* (n=2)
Blood and lymphatic system disorders	
Very common	Neutropenia* (n=146) Anaemia* (n=113) Thrombocytopenia* (n=91) Leukopenia* (n=48)
Immune system disorders	
Very common	Hypersensitivity[b] (n=28)
Metabolism and nutrition disorders	
Very common	Decreased appetite (n=95) Hypokalaemia (n=46) Hypomagnesaemia (n=45) Hypoalbuminaemia* (n=31)
Psychiatric disorders	
Very common	Insomnia* (n=32)
Nervous system disorders	
Very common	Neuropathy peripheral[n] (n=198) Dysgeusia* (n=46) Headache* (n=39)
Common	Dizziness* (n=25)
Cardiac disorders	

Common	Supraventricular tachycardia[d] (n=13)
Vascular disorders	
Very common	Haemorrhage[i] (n=85)
Gastrointestinal disorders	
Very common	Nausea (n=145) Diarrhoea* (n=107) Vomiting* (n=95) Abdominal pain* (n=85) Constipation (n=70) Mucosal inflammation* (n=68)
Uncommon	Pancreatitis* (n=2)
Skin and subcutaneous tissue disorders	
Very common	Rash* (n=93) Skin hyperpigmentation* (n=63) Dermatitis acneiform* (n=58) Dry skin* (n=56) Alopecia (n=55) PPES (n=41) Pruritus (n=36)
Common	Erythema (n=12) Hyperkeratosis* (n=7) Skin exfoliation (n=3)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia/Musculoskeletal pain* (n=84) Myopathy/Muscular disorder[l] (n=53) Back pain* (n=29)
Common	Pain in extremity* (n=25)
Renal and urinary disorders	
Common	Renal failure* (n=9)
General disorders and administration site conditions	

Very common	Fatigue* (n=140) Pyrexia* (n=82)
Infections and infestations	
Very common	Infections[o] (n=66)
Common	Upper respiratory tract infection* (n=20) Sepsis* (n=11)
Investigations	
Very common	Lipase increased* (n=61) Weight decreased (n=47) Transaminase increased* (n=44)
Common	Blood creatinine increased* (n=10) Amylase increased* (n=7)

Serious adverse event/deaths

Serious adverse events

A summary of all-causality SAEs by PT reported for >1% of participants in in the safety set is provided in Table 39.

Table 39: Summary of Serious Treatment-Emergent Adverse Events in ≥1% in the EC + mFOLFOX6 arm or EC-FOLFOX-P by PT (All Causalities) - Safety Set

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	**Grades**	**EC-FOLFOX-P (N= 259) n(%)**	**EC+ mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
Number of subjects with Serious TEAE	All Grades	119 (45.9)	12 (44.4)	107 (46.1)	89 (38.9)
	Grade 3+	106 (40.9)	11 (40.7)	95 (40.9)	74 (32.3)
Gastrointestinal disorders	All Grades	47 (18.1)	7 (25.9)	40 (17.2)	39 (17.0)
	Grade 3+	42 (16.2)	6 (22.2)	36 (15.5)	25 (10.9)
Intestinal obstruction	All Grades	11 (4.2)	0	11 (4.7)	5 (2.2)
	Grade 3+	11 (4.2)	0	11 (4.7)	3 (1.3)
Abdominal pain	All Grades	7 (2.7)	1 (3.7)	6 (2.6)	7 (3.1)
	Grade 3+	7 (2.7)	1 (3.7)	6 (2.6)	2 (0.9)
Vomiting	All Grades	7 (2.7)	1 (3.7)	6 (2.6)	1 (0.4)
	Grade 3+	7 (2.7)	1 (3.7)	6 (2.6)	1 (0.4)

		Phase 3 and SLI (Pooled)	SLI	Phase 3	
System Organ Class Preferred Term	**Grades**	**EC-FOLFOX-P (N= 259) n(%)**	**EC+ mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
General disorders and administration site conditions	All Grades	26 (10.0)	3 (11.1)	23 (9.9)	8 (3.5)
	Grade 3+	17 (6.6)	1 (3.7)	16 (6.9)	5 (2.2)
Pyrexia	All Grades	12 (4.6)	3 (11.1)	9 (3.9)	3 (1.3)
	Grade 3+	4 (1.5)	1 (3.7)	3 (1.3)	1 (0.4)
Disease progression	All Grades	8 (3.1)	0	8 (3.4)	1 (0.4)
	Grade 3+	8 (3.1)	0	8 (3.4)	1 (0.4)
Infections and infestations	All Grades	27 (10.4)	5 (18.5)	22 (9.5)	24 (10.5)
	Grade 3+	23 (8.9)	3 (11.1)	20 (8.6)	19 (8.3)
Sepsis	All Grades	5 (1.9)	1 (3.7)	4 (1.7)	1 (0.4)
	Grade 3+	5 (1.9)	1 (3.7)	4 (1.7)	1 (0.4)
Pneumonia	All Grades	3 (1.2)	0	3 (1.3)	5 (2.2)
	Grade 3+	3 (1.2)	0	3 (1.3)	5 (2.2)
Urinary tract infection	All Grades	4 (1.5)	1 (3.7)	3 (1.3)	2 (0.9)
	Grade 3+	2 (0.8)	1 (3.7)	1 (0.4)	2 (0.9)
Blood and lymphatic system disorders	All Grades	13 (5.0)	1 (3.7)	12 (5.2)	12 (5.2)
	Grade 3+	13 (5.0)	1 (3.7)	12 (5.2)	12 (5.2)
Anaemia	All Grades	8 (3.1)	0	8 (3.4)	1 (0.4)
	Grade 3+	8 (3.1)	0	8 (3.4)	1 (0.4)
Febrile neutropenia	All Grades	3 (1.2)	1 (3.7)	2 (0.9)	9 (3.9)
	Grade 3+	3 (1.2)	1 (3.7)	2 (0.9)	9 (3.9)
Respiratory, thoracic and mediastinal disorders	All Grades	8 (3.1)	0	8 (3.4)	6 (2.6)
	Grade 3+	7 (2.7)	0	7 (3.0)	6 (2.6)
Pulmonary embolism	All Grades	3 (1.2)	0	3 (1.3)	1 (0.4)
	Grade 3+	3 (1.2)	0	3 (1.3)	1 (0.4)
Nervous system disorders	All Grades	9 (3.5)	2 (7.4)	7 (3.0)	2 (0.9)
	Grade 3+	7 (2.7)	2 (7.4)	5 (2.2)	2 (0.9)
Syncope	All Grades	3 (1.2)	1 (3.7)	2 (0.9)	0
	Grade 3+	3 (1.2)	1 (3.7)	2 (0.9)	0
Investigations	All Grades	5 (1.9)	2 (7.4)	3 (1.3)	3 (1.3)
	Grade 3+	2 (0.8)	1 (3.7)	1 (0.4)	2 (0.9)
ALT increased	All Grades	3 (1.2)	0	3 (1.3)	1 (0.4)
	Grade 3+	1 (0.4)	0	1 (0.4)	1 (0.4)

Source: SCS, page 66

Death

Deaths during the study occurred in 39.7% of participants in the EC + mFOLFOX6 arm and 62.0% in the Control arm of the Safety Analysis Set. Disease under study was the most frequently reported case of death (32.8% and 55.0%, respectively).

On treatment deaths (i.e. deaths occurring ≤28 days after last dose of study treatment) were reported for 11 (4.7%) participants in the EC + mFOLFOX6 arm and 10 (4.4%) in the control arm; most on-treatment deaths were due to the disease under study.

A summary of Grade 5 TEAES is provided in Table S06. Of note, the applicant stated that all deaths in the EC-mFOLFOX6 arm were not related to the study medication.

Table 40: Summary of Grade 5 TEAEs

	Phase 3 and SLI (Pooled)	**SLI**	**Phase 3**	
Preferred Term	**EC-FOLFOX-P (N= 259) n(%)**	**EC + mFOLFOX6 (N= 27) n(%)**	**EC+ mFOLFOX6 (N= 232) n(%)**	**Control (N= 229) n(%)**
Number of subjects with Grade 5 TEAE	12 (4.6)	2 (7.4)	10 (4.3)	10 (4.4)
Disease progression	6 (2.3)	0	6 (2.6)	1 (0.4)
Intestinal obstruction	2 (0.8)	0	2 (0.9)	0
Gastrointestinal perforation	1 (0.4)	0	1 (0.4)	0
Large intestine perforation	1 (0.4)	0	1 (0.4)	1 (0.4)
Tumour perforation	1 (0.4)	1 (3.7)	0	0
Generalised tonic-clonic seizure	1 (0.4)	1 (3.7)	0	0
General physical health deterioration	0	0	0	2 (0.9)
Sepsis	0	0	0	1 (0.4)*
Abdominal sepsis	0	0	0	1 (0.4)
Septic shock	0	0	0	1 (0.4)
Cardiac arrest	0	0	0	1 (0.4)
Dyspnoea	0	0	0	1 (0.4)
Pneumonia	0	0	0	1 (0.4)
Respiratory failure**	0	0	0	1 (0.4)

Laboratory findings / Vital signs

Haematology

The most frequently reported clinically notable shifts (defined as worsening from baseline by at least 2 grades or to ≥ Grade 3) in haematology parameters were mainly driven by the expected myelosuppressive effect impact of the mFOLFOX6 regimen.

The most frequent haematology and coagulation parameters that shifted from Grade ≤2 at baseline to Grade 3 post baseline (≥10% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (26.1%), anaemia (18.7%), and WBC decreased (10.9%) and in the Control Arm was neutrophil count decreased (25.2%).

The most frequent haematology and coagulation parameter that shifted from Grade ≤2 at baseline to Grade 4 post baseline (≥5% of participants) in the EC + mFOLFOX6 Arm and the Control Arm was neutrophil count decreased (11.3% and 9.0%, respectively

Clinical chemistry

Shifts from Grade ≤2 at baseline to Grade 3 or 4 at post-baseline chemistry laboratory values are provided in Table S07.

Table 41: Shift from Grade <= 2 at Baseline to Grade >= 3 Post-baseline (Chemistries) - Phase 3 Safety Set (Protocol C4221015)

Parameter	EC+mFOLFOX6			Control		
	N	Grade 3 n (%)	Grade 4 n (%)	N	Grade 3 n (%)	Grade 4 n (%)
Alanine aminotransferase increased	228	3 (1.3)	0	222	6 (2.7)	0
Alkaline phosphatase increased	219	5 (2.3)	1 (0.5)	215	3 (1.4)	0
Aspartate aminotransferase increased	229	3 (1.3)	0	221	4 (1.8)	1 (0.5)
Blood bilirubin increased	229	3 (1.3)	1 (0.4)	222	1 (0.5)	0
Creatinine increased	229	3 (1.3)	0	222	2 (0.9)	0
Hypercalcemia	229	0	0	221	1 (0.5)	0
Hyperglycemia	226	22 (9.7)	2 (0.9)	219	4 (1.8)	0
Hyperkalemia	229	1 (0.4)	0	220	0	0
Hypermagnesemia	229	5 (2.2)	1 (0.4)	221	1 (0.5)	0
Hypernatremia	229	0	2 (0.9)	222	0	2 (0.9)
Hypoalbuminemia	229	2 (0.9)	0	222	1 (0.5)	0
Hypocalcemia	228	6 (2.6)	3 (1.3)	221	4 (1.8)	1 (0.5)
Hypoglycemia	229	0	0	221	0	0
Hypokalemia	229	9 (3.9)	2 (0.9)	220	11 (5.0)	0
Hypomagnesemia	229	2 (0.9)	1 (0.4)	221	1 (0.5)	0
Hyponatremia	227	6 (2.6)	0	220	8 (3.6)	0
Lipase increased	220	92 (41.8)	26 (11.8)	209	57 (27.3)	3 (1.4)

ECG

A summary of ECG data is provided in the following table.

Table 42: Categorization of ECG Data - Phase 3 Safety Set

		EC+mFOLFOX6		Control	
Parameter	Criteria (units)	N	n (%)	N	n (%)
ECG MEAN HEART RATE (BEATS/MIN)	Increase from baseline > 25 % and to a value > 100 bpm	226	32 (14.2)	218	11 (5.0)
	Decrease from baseline > 25 % and to a value < 50 bpm	226	1 (0.4)	218	2 (0.9)
PR INTERVAL NOT OTHERWISE SPECIFIED (MSEC)	New > 280 ms	224	0	216	1 (0.5)
QRS INTERVAL NOT OTHERWISE SPECIFIED (MSEC)	New > 120 ms	226	10 (4.4)	218	5 (2.3)
QTCF - FRIDERICIA'S CORRECTION FORMULA NOT OTHERWISE SPECIFIED (MSEC)	New > 450 ms	226	73 (32.3)	218	24 (11.0)
	New > 480 ms	226	19 (8.4)	218	10 (4.6)
	New > 500 ms	226	9 (4.0)	218	2 (0.9)
	Increase from baseline > 30 ms	226	118 (52.2)	218	32 (14.7)
	Increase from baseline > 60 ms	226	27 (11.9)	218	7 (3.2)

Safety in special populations

Subgroup analyses for safety in special groups and situations are summarized in Table 43.

Table 43: Safety in Special Groups and Populations Conclusions

Intrinsic Factors **(Age, gender, race,)**	In the Phase 3 EC + mFOLFOX6 Arm, the overall incidence of all-causality AEs (all grades) was generally similar between age groups (<65 vs ≥65), sex (male vs female), and race groups (non-Asian vs Asian), with the incidence of individual PTs varying between each of these subgroups. Sample size limitations preclude definitive conclusions regarding safety in the <75 vs ≥75-year subgroup.
Age	In the EC-FOLFOX-P, the incidence of ADRs was similar between age groups (<65 vs ≥65 years), with some variations in specific ADRs. SAEs were more common in participants aged ≥65 years. Key differences (≥ 10% of difference in incidence) included: • ADRs more frequent in ≥65 years vs < 65 years: Neutropenia, anaemia, infection, weight decreased, and hypomagnesemia, • ADRs less frequent in ≥65 years vs < 65 years: Peripheral neuropathy, vomiting, constipation, acneiform dermatitis, myopathy, increased transaminases, and headache. Overall, the nature of more frequently reported adverse events varied significantly between the age groups. There were too few participants in the ≥75 years age group (N=16 in the EC + mFOLFOX6 P) to make interpretable data comparisons between the < 75 and ≥75 years age groups.
Gender	In the Phase 3 EC + mFOLFOX6 arm, no adverse events (AEs) were reported more frequently in male patients compared to female patients (difference ≥10%). However, several AEs were less common in males than females, including vomiting, nausea, anaemia, alopecia, decreased neutrophil count, neutropenia, mucosal inflammation, and headache. These gender-based differences in AE incidence did not match the patterns observed in the control arm.
Race	In the EC-FOLFOX-P, the incidence of some adverse drug reactions (ADRs) varied between Asian and non-Asian participants: • Higher incidence in Asian participants: Skin hyperpigmentation, decreased appetite, leukopenia, thrombocytopenia, increased transaminases, hypoalbuminaemia, and drug hypersensitivity.

	• Higher incidence in non-Asian participants: Fatigue, peripheral neuropathy, and diarrhoea. These differences, analyzed using a volcano plot, suggest potential variations in ADR reporting between Asian and non-Asian populations, with some patterns also observed in the control arm.
Renal Impairment	No specific covariate renal impairment analysis was performed with BREAKWATER data. A review of safety and tolerability data between patients with normal and mild renal impairment could not establish differences between the 2 groups.
Hepatic Impairment	No specific covariate hepatic impairment analysis was performed with BREAKWATER data. A review of safety and tolerability data between patients with normal and mild hepatic impairment could not establish differences between the 2 groups.

Safety related to drug-drug interactions

In the previous application for patients with previously treated mCRC, no interaction between encorafenib and cetuximab has been shown.

Part of this application for the use of EC + FOLFOX in previously untreated mCRC, the potential interaction of encorafenib with oxaliplatin was assessed and no drug-drug interactions were evidenced. In addition, the metabolism of 5-fluorouracile, and leucovorin is not mediated by CYP450 enzymes, and the risk of CYP450-mediated DDI of encorafenib with these agents is expected to be low. No clinical differences in encorafenib exposures were evidenced when encorafenib in given with or without mFOLFOX6. (see the clinical pharmacology section).

No participants with AEs of drug interactions were identified in the Phase 3 portion of BREAKWATER, as defined by the following MedDRA HLT: Interactions.

Dose reduction / dose interruption / discontinuation due to adverse events

Dose interruption and dose reduction

All-causality AEs associated with dose interruption of any study drug occurred in 91.4% of participants in the EC + mFOLFOX6 arm and 73.4% in the Control arm.

The most frequent (≥10% of participants) AEs associated with dose interruption of any study drug in the EC + mFOLFOX6 arm were neutrophil count decreased (19.4%), neutropenia (16.4%), pyrexia (15.1%), neuropathy peripheral (12.1%), anaemia (11.6%), and COVID-19 and peripheral sensory neuropathy (11.2% each). In the Control arm they were neutrophil count decreased (13.1%) and neutropenia (11.4%).

All-causality AEs associated with dose interruption of encorafenib occurred in 67.7% (47.4% for Grade ≥3 events) of participants in the EC + mFOLFOX6 arm; the most frequent (≥5% of participants) AEs associated with dose interruption of encorafenib in the EC + mFOLFOX6 arm were anaemia (9.1%), pyrexia (8.6%), COVID-19 (7.8%), neutropenia (6.9%), neutrophil count decreased (6.5%), and diarrhoea (5.2%).

All-causality AEs associated with dose interruption of cetuximab occurred in 72.4% (52.6% for Grade ≥3 events) of participants in the EC + mFOLFOX6 arm; the most frequent (≥5% of participants) AEs associated with dose interruption of cetuximab in the EC + mFOLFOX6 arm were

neutrophil count decreased (15.1%), neutropenia (12.9%), anaemia (9.9%), COVID 19 (9.9%), pyrexia (8.6%), platelet count decreased (7.8%) and thrombocytopenia (5.6%)

All-causality AEs associated with dose interruption of other study drugs occurred in 84.5% (Grade ≥ 3: 57.8%) of participants in the EC + mFOLFOX6 arm and 73.4% (Grade ≥3: 38.0%) in the Control arm

The most frequent (≥10% of participants) AEs associated with dose interruption of other study drugs in the EC + mFOLFOX6 arm were neutrophil count decreased (15.9%), neutropenia (13.4%), neuropathy peripheral (12.1%), peripheral sensory neuropathy (11.2%), and pyrexia (10.8%), In the Control arm they were neutrophil count decreased (13.1%) and neutropenia (11.4%).

In the Phase 3 part of the BREAKWATER study, the percentage of patients with an adverse event leading to dose reduction of any study drug of the regimen was 65.5% in the EC + mFOLFOX6 arm (encorafenib 25.4%, cetuximab 9.1 % and 59.9% mFOLFOX6) and in the Control arm it was 54.1%.

The proportion of patients in the EC + mFOLFOX6 arm, who had Grade ≥3 AEs leading to dose reduction of any study drug was similar to that observed in the Control arm (25.9% and 21.0%, respectively).

Neutrophil count decreased (12.1%), neutropenia (10.3%), neuropathy peripheral (7.3%), peripheral sensory neuropathy (6.0%), platelet count decreased (5.6%) anaemia, asthenia and neurotoxicity (5.2% each) led to dose reduction of any study drug in ≥ 5.0% of patients in the EC + mFOLFOX6 arm, and in the Control arm AEs leading to dose reduction were neutropenia (11.4%), neutrophil count decreased (10.9%), peripheral sensory neuropathy (7.4%), neuropathy peripheral (6.6%) and diarrhoea (6.1%).

Adverse events leading to discontinuation of treatment

Table 44 provides a summary of TEAEs associated with permanent discontinuation of encorafenib, cetuximab or chemotherapy. The only AEs leading to discontinuation of encorafenib (≥ 2.0% of patients) by PT in the EC + mFOLFOX6 arm was lipase increased (2.2%).

Table 44: Summary of TEAE Associated with Permanent Discontinuation of Encorafenib, cetuximab or any other drug by PT and Maximum CTCAE Grade in≥1% BREAKWATER EC+mFOLFOX6 or control Arm (All Causalities) - Phase 3

	EC + mFOLFOX6 arm N=232			**Control arm N=229**
Any study drug n(%) Grade3+ n(%)	**62(26.7%)/36(15.5%)**			**40(17.5%)/36(15.7%)**
By drug	**Encorafenib**	**Cetuximab**	**Other study drug**	**Other study drug**
With any AE n(%) /Grade3+n(%)	32(13.8)/20(8.6)	34(14.7)/24(10.3)	48(20.7)/27(11.6)	40(17.5)/36(15.7)
Asthenia	2(0.9)/1(0.4)	2(0.9)/1(0.4)	6(2.6)/1(0.4)	1(0.4)/0
Anaemia	1(0.4)/1(0.4)	2(0.9)/2(0/9)	5(2.2)/4(1.7)	0/0

Decreased appetite	1(0.4)/ 1(0.4)	0/0	3(1.3)2(0.9)	0/0
Disease progression*	3(1.3)/3(1.3)	3(1.3)/3(1.3)	3(1.3)/3(1.3)	1(0.4)/1(0.4)
Fatigue	0/0	0/0	2(0.9)/0	1(0.4)/1(0.4)
hypersensitivity	2(0.9)/1(0.4)	2(0.9)/1(0.4)	3(1.3)/1(0.4)	
Infusion related reaction	1(0.4)/0(0.0)	3(1.3)/2(0.9)	0/0	0/0
ILD	1(0.4)/1(0.4)	1(0.4)/1(0.4)	2(0.9/1(0.4)	
Intestinal obstruction	2(0.9)/2(0.9)	2(0.9)/2(0.9)	2(0.9)/2(0.9)	5(2.2)/4(1.7)
Lipase increased	5(2.2)/1(0.4)	5(2.2)/1(0.4)	0/0	0/0
Nausea	1(0.4)/0	1(0.4)/0	2(0.9)/0	1(0.4)/1(0.4)
Neutrophil count decreased	0	0	2(0.9)/0	1(0.4)/1(0.4)
Peripheral sensory neuropathy	2(0.9)/1(0.4)	2(0.9)/1(0.4)	3(1.3)/1(0.4)	0
Platelet count decreased	0/0	0/0	3(1.3)/0(0.0)	1(0.4)/0(0.0
pyrexia	0/0	0/0	2(0.9)/1(0.4)	0
Sepsis	1(0.4)/1(0.4)	2(0.9)/2(0.9)	2(0.9)/2(0.9)	1(0.4)/1(0.4)
Urinary tract infection	0/0	0/0	3(1.3)/0(0.0)	1(0.4)/0(0.0
General physical health deterioration	0/0	0/0	0/0	3(1.3)/2(0.9)

Post marketing experience

Post-marketing experience has been gained with the EC combination in BRAF V600E-mutant mCRC, as well as with encorafenib in combination with binimetinib in the other approved indications of encorafenib and is described in periodic aggregate reports that the Applicant has submitted to regulatory authorities.

Since the initial MAA of encorafenib, the Applicant submitted ten (10) Periodic Benefit Risk Evaluation Reports (PBRER/PSUR) to the EMA. PBER 10 covers the period going from 27 June 2024 through to 26 June 2025 and was submitted to EMA on 02 September 2025. As of 26 June 2025 (Data Lock Point (DLP) of the most recently submitted PBRER, encorafenib has received regulatory approval in 69 countries and was marketed in 47 countries.

Since first marketing approval, (27-Jun-2018 in USA and 20 September 2018 in Europe) and as of 26 June 2025, cumulatively, the worldwide exposure to encorafenib is estimated to be 40,669 patient-years.

During the reporting intervals of the PBRERs, no significant new safety findings have been identified which alter the characterisation of previously recognised important identified risks, important potential risks or missing information, as listed in the approved Risk Management Plan version 3.0.

Based on the evaluation of the cumulative safety data presented in the PBRERs and the benefit-risk analysis, the MAHs did not propose any safety-related changes to the reference safety information or changes to risk minimization measures at the time of the last submitted PBRER.

2.7.1. Discussion on clinical safety

The safety data is mainly based on parts of study C4221015 (BREAKWATER study, EC-mFOLFOX6-P):

- Cohort 2 - EC in combination with mFOLFOX6 from the Safety lead in (SLI) portion of BREAKWATER up to the data cutoff date of 22 December 2023 (N=27). The SLI was conducted in patients with BRAF V600E-mutant mCRC with 0-1 prior systemic therapy regimen in the metastatic setting
- Randomized Phase 3 portion of the BREAKWATER study, which is described to summarize the safety of the combination of encorafenib + cetuximab with mFOLFOX6 and of a Control arm (including standard of care therapies) in patients with previously untreated BRAF V600E-mutant mCRC, up to the data cutoff date of 06 January 2025 (N=232 for the EC + m FOLFOX6 arm and N = 229 for the Control arm)

Regarding the Phase 3 portion of the BREAKWATER study, 232 participants were exposed to the combination of encorafenib 300mg QD with cetuximab 500 mg/m^2 Q2W and mFOLFOX6. In the control arm (229 participants), all participants received oxaliplatin, with 71% of participants receiving a 5-FU+oxaliplatin based chemotherapy regimen (47.3% FOLFOX and 23.7% FOLFOXIRI), and the remaining participants received CAPOX. More than eighty percent (81.1 %) participants received bevacizumab in the control arm.

The median duration of exposure to study treatment was 11.45 months in the EC + mFOLFOX6 arm (N=232) and 5.95 months (in the Control arm (N=229), with 28.4%, and 6.6% of participants respectively, still receiving study treatment at the time of the data cutoff.

Of note, the median duration of exposure to oxaliplatin was shorter compared to that of the overall study treatment regimen in the EC + mFOLFOX6 arm (21.3 weeks vs 49.8 weeks) and in the Control arm (19.0 weeks vs 25.9 weeks).

Treatment emergent adverse events of any grade occurred in 100% and 99.1% of patients in the EC + mFOLFOX6 arm and the Control arm.

The most frequently reported AEs of all grades in patients treated with EC + mFOLFOX6 were gastrointestinal disorders (87.1%), nervous system disorders (82.3%), skin and subcutaneous tissue disorders (81.0%), general disorders and administration site conditions (80.6%), investigations (70.7%), blood and lymphatic system disorders (62.5%), metabolism and nutrition disorders (62.1%), musculoskeletal and connective tissue disorders (57.3%), infections and infestations (53.0%).

Grade 3-4 events occurred in 85.8 % and 71.2% of patients in the EC + mFOLFOX6 arm and in the Control arm, SAEs in 46.1% respectively in 38.9%.

On treatment deaths (i.e. deaths occurring ≤28 days after last dose of study treatment) were reported for 11 (4.7%) participants in the EC + mFOLFOX6 arm and 10 (4.4%) in the control arm; most on-treatment deaths were due to the (progressive) disease under study.

The existing list of ADRs from EC as determined for the MAA in previously treated mCRC population and defined based on the safety data of BEACON CRC served as the background for the determination of ADRs for the current application.

The most common ADRs (≥25%) of EC + mFOLFOX6 as determined in the EC-mFOLFOX6-P population of BREAKWATER were:

Neuropathy peripheral (76.4%), neutropenia (56.4%), nausea (56.0%), fatigue (54.1%), anaemia (43.6%), diarrhoea (41.3%), vomiting and decreased appetite (36.7% each), rash (35.9%), thrombocytopenia (35.1%), abdominal pain and haemorrhage (32.8% each), arthralgia (32.4%) and pyrexia (31.7%), constipation (27.0%) mucosal inflammation (26.3%) and infection (25.5%).

As compared to EC, several new ADRs were reported for EC+mFOLFOX6:

Neutropenia, leukopenia, thrombocytopenia, mucosal inflammation, hypoalbuminaemia, weight decreased and infection, and the common ADRs of hypokalaemia, hypomagnesaemia, upper respiratory tract infection, and sepsis.

In addition, some toxicities increased in frequency in EC + mFOLFOX6 as compared to the known safety profile of EC. The slightly worse safety profile of the new combination might be one the one hand due to the addition of mFOLFOX6 but on the other hand also due to a longer exposure to EC in BREAKWATER as compared to BEACON CRC.

Section 4.8 of the SmPC was adapted accordingly and Table 5 in this section has been expanded to include a new column, and the descriptions of selected adverse reactions have been updated to include relevant new information.

The most frequent haematology parameter that shifted from Grade ≤2 at baseline to Grade ≥3 post baseline (≥10% of participants) in the EC + mFOLFOX6 Arm as well as in the control arm was neutrophil count decreased (26.1% resp. 25.2%). These reported clinically notable shifts in haematology parameters were mainly driven by the expected myelosuppressive effect impact of the mFOLFOX6 regimen.

Chemistry laboratory findings reported at the high rates were hypokalaemia and hypomagnesemia, that are known side effects of EGFR inhibitors and are addressed in the cetuximab labelling information. Of note, the slightly higher incidence of QT prolongation events in the BREAKWATER study in comparison to BEACON study might be attributable to hypokalaemia.

Lipase increased was identified in 24% of patients and was the leading cause of dose modifications and discontinuation of encorafenib, occurring in 1.7% in patients who discontinued the treatment and 2.6% of patients required dose reduction. However, of note, the incidence of acute symptomatic pancreatitis was very low.

The overall incidence of all-causality AEs (all grades) was generally similar between age groups (<65 vs ≥65), sex (male vs female), and race groups (non-Asian vs Asian), with the incidence of individual PTs varying between each of these subgroups.

In summary, the toxicities of EC + mFOLFOX6 remained manageable (e.g. as indicated by a high median relative dose intensity for all components of the combination) notably when compared to the Control therapy used in the Phase 3 of BREAKWATER, which is the standard of care for the first line treatment of BRAF-V600E mutated mCRC patients. No new safety concerns were identified.

2.7.2. Conclusions on clinical safety

The safety assessment of the EC + mFOLFOX6 treatment combination is based primarily on the safety population of 259 patients with BRAF V600E-mutant mCRC who received the investigational regimen in the Phase III BREAKWATER study (SLI and phase 3).

The overall size of the safety population and the duration of exposure to the investigational treatment are considered sufficient to characterize the safety profile of the combination.

Based on the review of the safety data, there were no important new safety signals identified. Overall, the safety profile of the combination was generally consistent with the known safety profiles of the individual regimen components (BRAF inhibitors, EGFR inhibitors, FOLFOX) when administered individually.

Of note, due to the heterogeneity of the control arm, the safety assessment was somewhat complicated and has to be carefully considered.

2.7.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the RMP version 4.0 is acceptable.

Safety concerns

Table 45: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Secondary skin neoplasms: cuSCC and new primary melanoma
Important potential risks	- QT prolongation - Non-cutaneous malignancies with RAS mutation - Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors - Over-exposure in patients
Missing information	- Use in patients with severe renal impairment

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities for encorafenib.

Risk minimisation measures

Table 46: Summary table of pharmacovigilance activities and risk minimisation activities for safety concerns of encorafenib.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks for encorafenib		
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Routine: Warning in Section 4.4 of the SmPC and relevant PIL section Listed in Section 4.8 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Important potential risks for encorafenib		
QT prolongation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Non-cutaneous malignancies with RAS mutation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Routine: Warning in sections 4.2 and 4.4 of the SmPC and relevant PIL sections Discussion in section 4.5 Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Over-exposure in patients with moderate to severe hepatic impairment	Routine:	Routine Additional: none

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Dose modification recommendations in section 4.2 of the SmPC and PIL relevant section Warning in section 4.4 and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	
Missing information for encorafenib		
Use in patients with severe renal impairment	Routine: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none

2.9. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly.

The version 4.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Approved indication is:

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. For biomarker-based patient selection, see section 4.2.

3.1.1. Disease or condition

Colorectal cancer (CRC) is one of the most common malignancies worldwide and remains a major cause of cancer-related mortality. Approximately one quarter of patients with CRC present with metastatic disease at initial diagnosis, and close to 50% will develop metastases during the course of their illness (Cervantes et al., 2022), accounting for 250,000 deaths in the EU in 2020 (ECIS 2024). Approximately 8-10% of patients with mCRC harbour a BRAF V600E mutation (Tabernero et al., 2022). BRAF V600E-mutant CRC represents a distinct molecular subtype characterised by right-sided primary tumours and an overall poor prognosis (Takeda et al., 2021).

3.1.2. Available therapies and unmet medical need

BRAF and RAS alterations are generally mutually exclusive molecular subsets in CRC (Clarke et al., 2015).

First line treatment options for patients with Stage IV pMMR unresectable BRAF V600E-mutant CRC include chemotherapy doublet (mFOLFOX6; CAPOX; FOLFIRI) or, for fit patients with right-sided tumours, triplet combination (FOLFOXIRI) with or without bevacizumab (Cervantes et al, 2022).

In the 2nd- and later-line setting, encorafenib with cetuximab was approved in the EU for the respective population in 2020 based on the RCT BEACON CRC (Kopetz et al., 2019) resembling the therapeutic standard in previously treated patients.

The presence of BRAF V600E mutation is associated with poor prognosis. In a recent study, patients receiving first-line chemotherapy with or without bevacizumab had a median PFS of 6.0 months and a median OS of 12.9 months. Despite current available treatments, the unmet medical need in this population remains high.

3.1.3. Main clinical studies

Single pivotal study C4221015 (BREAKWATER) is an ongoing multiregional, randomised controlled, open-label Phase III trial comparing encorafenib plus cetuximab plus mFOLFOX6 (Arm B) with investigator's-choice standard oxaliplatin-based chemotherapy (mFOLFOX6, FOLFIRI, FOLFOXIRI with or without bevacizumab) as first-line treatment for patients with BRAF V600E-mutant metastatic CRC.

Dual primary endpoints are PFS and ORR by blinded independent central review, while OS is a key secondary endpoint. Treatment continued until centrally confirmed disease progression, unacceptable toxicity, withdrawal of consent, or death, with subsequent survival follow-up.

The efficacy analyses presented are based on the PFS DCO of 06 January 2025. At this cut-off, deaths had occurred in 94 patients in the EC+mFOLFOX6 arm and 148 patients in the control arm.

3.2. Favourable effects

- Median OS was 30.3 months (95% CI: 21.7, NE) in the EC+mFOLFOX6 arm vs 15.1 months (95% CI: 13.7, 17.7) in the control arm (HR 0.49; 95% CI: 0.375, 0.632, one-sided p<0.0001).
- Median PFS per BICR was 12.8 months (95% CI: 11.2, 15.9) in the EC+mFOLFOX6 arm vs 7.1 months (95% CI: 6.8, 8.5) in the control arm (HR 0.53; 95% CI: 0.407, 0.677; one-sided p<0.0001).
- ORR by BICR was 60.9% (95% CI: 51.6, 69.5) in the EC+mFOLFOX6 arm vs 40.0% (95% CI: 31.3, 49.3) in the control arm (odds ratio 2.443; 95% CI: 1.348, 4.380; one-sided p=0.0008) based on ORR DCO of 22 December 2023.

The PFS effect was consistently observed across clinically relevant subgroups and was supported by RMST analyses, analyses using a treatment-policy strategy, unstratified regression analyses and PFS by investigator assessment.

The OS effect was consistently observed across clinically relevant subgroups and sensitivity and supplementary analyses were supported by an acceptable subsequent EC therapy exposure in the control arm.

3.3. Uncertainties and limitations about favourable effects

Only patients with BRAF V600E-mutant, RAS wild-type, microsatellite-stable (MSS/pMMR) tumours were enrolled. Consequently, extrapolation of the treatment effects to populations with RAS co-mutations or to MSI-H/dMMR disease is limited.

Encorafenib monotherapy was not directly evaluated, with its lack of efficacy inferred from preclinical and early clinical data. The choice of the encorafenib–cetuximab doublet and exclusion of binimetinib relied mainly on evidence from the later-line BEACON trial. In BREAKWATER, comparisons of the EC doublet and EC+mFOLFOX6 triplet with standard of care explored the added value of chemotherapy.

A discrepancy between BICR and investigator-assessed PFS was observed (20.8% in the EC+mFOLFOX6 arm and 13.2% in the control arm), which warrants consideration in the interpretation of the PFS results.

The overall survival in the control arm was unexpectedly low, without clear improvement compared with historical first-line outcomes predating the availability of encorafenib plus cetuximab in later-line therapy.

3.4. Unfavourable effects

Grade 3-4 events occurred in 85.8 % of patients in the EC + mFOLFOX6 arm and in 71.2% of the control arm, while SAEs were reported in 46.1% and 38.9% of patients, respectively. The higher frequency of severe toxicity observed in the EC + mFOLFOX6 arm was considered consistent with the addition of combination therapy.

On-treatment deaths (i.e. deaths occurring ≤28 days after the last dose of study treatment) were reported for 11 (4.7%) participants in the EC + mFOLFOX6 arm and 10 (4.4%) in the control arm; most on-treatment deaths were attributable to progressive disease.

The most common ADRs (≥25%) of EC + mFOLFOX6 in the EC-FOLFOX-P population of BREAKWATER were: neuropathy peripheral (76.4%), neutropenia (56.4%), nausea (56.0%), fatigue (54.1%), anaemia (43.6%), diarrhoea (41.3%), vomiting and decreased appetite (36.7% each), rash (35.9%), thrombocytopenia (35.1%), abdominal pain and haemorrhage (32.8% each), arthralgia (32.4%) and pyrexia (31.7%), constipation (27.0%) mucosal inflammation (26.3%) and infection (25.5%).

Compared to EC alone, additional ADRs and increased frequencies of known toxicities were observed with EC+mFOLFOX6 consistent with the addition of mFOLFOX6. No new unexpected safety concerns were identified.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 47: Effects Table for Braftovi in combination with cetuximab and FOLFOX for the 1st line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation (DCO for ORR 22 December 2023; DCO for PFS and OS 06 Jan 2025)

Effect	Short description	Unit	Treatment (95% CI)	Control (95% CI)	Odds ratio/ Hazard ratio (95% CI)
Favourable Effects					
PFS	Progression-Free Survival by BICR	Median, months	12.8 (11.2, 15.9)	7.1 (6.8, 8.5)	HR 0.53 (0.407, 0.677) p<0.0001
OS	Overall Survival	Median, months	30.3 (21.7, NE)	15.1 (13.7, 17.7)	HR 0.49 (0.375; 0.632) p<0.0001
Unfavourable Effects					
Grade ≥3 AE	Incidence of adverse events of grade 3 or 4	(%)	85.8	71.2	
SAEs	Incidence of serious adverse events	(%)	46.1	38.9	
AEs leading to discontinuation of all study treatment	Incidence of discontinuations due to adverse events	(%)	6.9	17.0	
AEs leading to death	Incidence of AEs leading to death	(%)	4.3	4.4	

Abbreviations: DCO=data cut off; ORR= Objective Response Rate; BICR= Blinded independent central review; OR=Odds ratio; HR=Hazard ratio; PFS=Progression free survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The single pivotal study met both dual primary endpoints, ORR and PFS by BICR, as well as the key secondary endpoint OS, demonstrating statistically significant and clinically meaningful effect sizes.

The robustness of the efficacy results was supported by consistent effects across clinically relevant subgroups and concordant findings in sensitivity and supplementary analyses for both primary and secondary endpoints. The interpretation of the OS results was not considered to be meaningfully impacted by the rate of dose modifications for encorafenib and the rate of administration of post-protocol encorafenib/cetuximab therapy in the control arm.

The efficacy of encorafenib plus cetuximab (EC) combination had previously been established in the later-line BEACON CRC study. The incremental contribution of chemotherapy to EC was addressed in the pivotal BREAKWATER study showing numerical higher ORR, longer PFS and OS in favour of the EC+mFOLFOX6 combination compared to EC. Numerically, EC was inferior for PFS compared to SOC.

Based on the review of the safety data of the pivotal study, the toxicities associated with EC + mFOLFOX6 were considered manageable despite a higher incidence of Grade 3-4 adverse events compared with the control arm. This was supported by the maintenance of a high median relative dose intensity for all components of the combination notably when compared to the control therapy used in the Phase 3 of BREAKWATER (although there was a heterogeneity within the control arm). No important new safety concerns were identified.

3.7.2. Balance of benefits and risks

The efficacy results from the single pivotal trial C4221015 (BREAKWATER) in patients with BRAF V600E-mutant mCRC were considered clinically meaningful, demonstrating substantial improvements in PFS, and in particular, OS.

Although the toxicities associated with EC-mFOLFFOX6 were increased compared with the control arm, they were considered manageable and consistent with the addition of combination therapy. No important new safety concerns were identified.

Overall, the benefit-risk balance of encorafenib in combination with cetuximab and FOLFOX in the proposed indication is considered favourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit-risk of Braftovi in the newly proposed indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include, in combination with cetuximab and FOLFOX, the first line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation for BRAFTOVI, based on the interim results from the pivotal Study C4221015 (BREAKWATER). This is an open-label, multicenter, 3-arm, randomized Phase 3 study of encorafenib plus cetuximab (EC) alone or in combination with mFOLFOX6 versus standard of care chemotherapy in first-line participants with BRAF V600E-mutant mCRC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The version 4.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.