21 May 2026
EMADOC-1700519818-2963495
Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Erbitux

International non-proprietary name: cetuximab

Procedure No. EMA/VR/0000327014

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	Term
1L	first-line
2L	second-line
5-FU	5-fluorouracil
AA	Accelerated Approval
ADAM	Analysis Data Model
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BICR	blinded independent central review
BID	twice daily
BIMO	Bioresearch Monitoring Information
BOR	best overall response
bpm	beats per minute
BRAF	serine/threonine-protein kinase B-Raf
BRAF	B-RAF proto-oncogene, serine/threonine-protein kinase
BRAFi	serine/threonine-protein B-Raf inhibitor
BSC	best supportive care
BTD	Breakthrough Therapy Designation
BTDR	Breakthrough Therapy Designation Request
CAPOX	capecitabine/oxaliplatin
CDx	companion diagnostic
cfDNA	circulating free DNA
CI	confidence interval
CO	Clinical Overview
COVID-19	coronavirus disease 2019

CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctMoniTR	circulating tumor DNA for monitoring treatment response
CTR	Clinical Trials Register
d	day
D5W	dextrose 5% in water
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
EC	ethics committee; encorafenib + cetuximab
ECG	electrocardiogram or electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EP	endpoint
ER	exposure-response
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOLFIRI	5-fluorouracil/leucovorin (folinic acid)/irinotecan
FOLFOX	5-fluorouracil/leucovorin (folinic acid)/oxaliplatin
FOLFOXIRI	5-fluorouracil/leucovorin (folinic acid)/oxaliplatin/irinotecan
FPFV	first patient first visit
FU	fluorouracil

GI	gastrointestinal
HLT	high level term
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
IAP	Integrated Analysis Plan
IFL	irinotecan, fluorouracil, and leucovorin
IND	Investigational New Drug
INR	international normalized ratio
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	intravenous(ly)
JSMO	Japanese Society of Medical Oncology
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homologue
LGX818	encorafenib
LV	leucovorin
mCRC	metastatic colorectal cancer
mDOR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase kinase
mFOLFOX6	modified FOLFOX-6
mo	months
MSI-H	microsatellite instability-high
mTTP	median time to progression
N	number
NA	Not Available
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NDA	New Drug Application

NE	not estimable
NEC	not elsewhere classified
NR	not reached
NRAS	NRAS proto-oncogene, GTPase
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PADER	Periodic Adverse Drug Experience Report
PCD	primary completion date
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PMA	premarket approval
PMR	postmarketing requirement
PO	oral
PR	partial response
PS	performance status
PT	Preferred Term
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
Q6W	once every 6 weeks
QD	once daily
QT	QT interval
QTcF	QTc corrected using Fridericia's formula
QW	once weekly
PFS2	progression-free survival 2
RAF	serine/threonine-protein kinase
RAS	rat sarcoma viral oncogene homologue
RCI	repeated confidence interval

RECIST	Response Evaluation Criteria in Solid Tumors
RGQ	Rotor-Gene Q
RMST	restricted mean survival time
RTOR	Real-time Oncology Review
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SBS	Summary of Biopharmaceutic Studies
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SDTM	Study Data Tabulation Model
SLI	Safety Lead-in
SN	sequence number
sNDA	Supplemental New Drug Application
SOC	standard-of-care; System Organ Class
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
TTP	time to progression
TTR	time to response
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
v	version
vs	versus
WBC	white blood cell
WHO	World Health Organization
wk	weeks
WRO	written response only
WT	wild-type

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Europe B.V. submitted to the European Medicines Agency on 3 February 2026 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.6.a	C.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 encorafenib and mFOLFOX6 treatment of metastatic colorectal cancer with a BRAF V600E mutation for ERBITUX, based on interim results from study C4221015 (BREAKWATER); this is an open-label, multicenter, 3-arm, randomized phase 3 study of EC alone or in combination with mFOLFOX6 versus standard-of-care chemotherapy in first-line participants with BRAF V600E-mutant mCR. As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.1 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2025 on the granting of a class 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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Filip Josephson

Timetable	Actual dates
Submission date	3 February 2026
Start of procedure:	21 February 2026

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report circulated on:	17 April 2026
PRAC Rapporteur's preliminary assessment report circulated on:	17 April 2026
Joint Rapporteur's updated assessment report circulated on:	13 May 2026
CHMP opinion:	21 May 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The claimed therapeutic indication in this procedure is:

Erbitux is indicated for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer

- in combination with encorafenib and mFOLFOX6,

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

Cetuximab is a chimeric monoclonal IgG1 antibody that is specifically directed against EGFR (also known as ErbB1 or HER1). EGFR signaling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration, and cellular invasion/metastasis. Cetuximab binds to the extracellular domain of EGFR with high affinity and blocks binding of endogenous EGFR ligands, resulting in inhibition of dimerization and thus endogenous signaling and receptor function. It further induces the internalization of EGFR, which can lead to downregulation of the receptor. Cetuximab also targets cytotoxic immune effector cells toward EGFR-expressing tumor cells (antibody dependent cell-mediated cytotoxicity, cetuximab

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 for Braftovi in the EU in 2020. This randomised, open-label, three-arm phase 3 trial compared encorafenib plus cetuximab, with or without binimetinib, against investigator's choice of standard of care (irinotecan plus cetuximab or FOLFIRI plus cetuximab). The study met its primary endpoint, demonstrating an improvement in overall survival: median OS was 9.3 months with encorafenib plus cetuximab versus 5.9 months with standard of care (HR 0.61; 95% CI 0.48–0.77). The incremental contribution of binimetinib to the triplet regimen was limited, with no clinically relevant advantage over the doublet combination.

Approved indication as part of this application is:

Erbitux is indicated for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer

- in combination with encorafenib and FOLFOX for the first line treatment.

For details, see section 5.1. For biomarker-based patient selection, see section 4.2.

In combination with encorafenib and FOLFOX, Erbitux is administered once every other week. Each dose is 500 mg cetuximab per m^2 body surface area.

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

The Sponsor received Scientific Advice on the development of Encorafenib for first line treatment of metastatic colorectal cancer from the CHMP on 23 July 2020 (EMEA/H/SA/3177/3/2020/II). 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 tp support and 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 adminstration

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Cetuximab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Therefore, no Environmental Risk Assessment studies are required for cetuximab.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of cetuximab.

- Considering the above data, cetuximab is not expected to pose a risk to the environment.

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.

2.3.2. Pharmacokinetics

There were no clinical pharmacology analyses done on cetuximab in the BREAKWATER study. No cetuximab PK sampling were included in BREAKWATER.

The BREAKWATER study included PK sampling of encorafenib which is the active substance in Braftovi. The Applicant performed several PK and exposure-response analyses based on the PK data for encorafenib for participants with BRAF V600E-mutant mCRC which are summarized as follows:

- Encorafenib PK (plasma concentration profiles and PK parameters) in the BREAKWATER study were consistent with historical data of encorafenib in adult patients with BRAF V600E-mutant mCRC after prior therapy.

- Encorafenib PK from BREAKWATER were well characterized by a 2-compartment population PK model with first-order absorption and elimination. Covariates in the final model, including body weight, tumor type, and age, had no clinically relevant effects on the plasma PK of encorafenib.
- ER analyses were performed using encorafenib plasma exposure metrics and primary efficacy endpoints. No statistically significant relationships were found.
- ER analyses were performed using encorafenib plasma exposure metrics and safety endpoints. Safety endpoints included all-causality, all-grade AEs with frequency of ≥25%; any Grade 3 or higher AEs; and all-grade AESIs. ER analyses for safety endpoints found no statistically significant relationships, except for the relationship between asthenia and log-transformed average encorafenib plasma concentration over the first 24 hours and any Grade 3 or higher AE and average encorafenib plasma concentration over the first 24 hours. The majority of asthenia events were Grade 1 and 2 in severity and dose modifications associated with asthenia rarely occurred. The current label for encorafenib provides detailed guidance for dose modifications for Grade 3 or higher AEs for specific AEs. Overall, these findings do not have additional labelling implications.
- Participants receiving encorafenib with oxaliplatin (EC + mFOLFOX6) had no evidence of overt changes in oxaliplatin PK, measured as platinum in plasma and platinum in ultrafiltrate, indicating the absence of a drug-drug interaction risk between encorafenib and oxaliplatin.

2.3.3. Discussion on clinical pharmacology

The BREAKWATER study did not include PK sampling of cetuximab which is considered a limitation in this submission. However, this is acceptable since the BREAKWATER study included efficacy and safety data in a reasonable number of patients to assess the benefit-risk of the combination (encorafenib [E]+cetuximab [C]) in the target population.

No Cetuximab plasma sampling for PK was performed in BREAKWATER 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 E+C 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 E+C 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.

Without any cetuximab PK data in the target population, it is not possible to confirm that PK is similar between adult patients with BRAF V600E mutant metastatic colorectal cancer (first-line setting) and the other approved indications/target populations. However, the probability that the cetuximab PK profile would be different for metastatic colorectal cancer in the first-line setting is low. No clinically relevant differences in cetuximab PK have been noted for other indications/target populations (e.g. including squamous cell cancer of the head and neck [see procedure Erbitux-H-C-558-II-0005]).

Without any cetuximab PK data in BREAKWATER, it is not possible to confirm the absence of PK DDIs. However, since cetuximab is a monoclonal antibody, the likelihood of clinically relevant PK DDIs is low both from the object and precipitant perspective. Regarding the combination with encorafenib, no PK DDI is expected; Co-administration of encorafenib did not lead to any clinically relevant changes in the cetuximab PK-profile based on previously submitted PK data from the BEACON Study (see Braftovi

procedure EMEA/H/C/xxxx/WS/1695). Similarly, mFOLFOX6 is not likely to have any relevant impact on the cetuximab PK profile. The combination with FOLFOX is already included in the existing Erbitux SmPC (for treatment of patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer). Of note, from a precipitant perspective, cetuximab was not shown to lead to any clinically significant changes in the encorafenib PK-profile, based on enforafenib PK data which were collected in the BREAKWATER study.

2.3.4. Conclusions on clinical pharmacology

No new clinical pharmacological data are provided in the current submission which is acceptable since sufficient efficacy and safety data have been collected in the target population.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

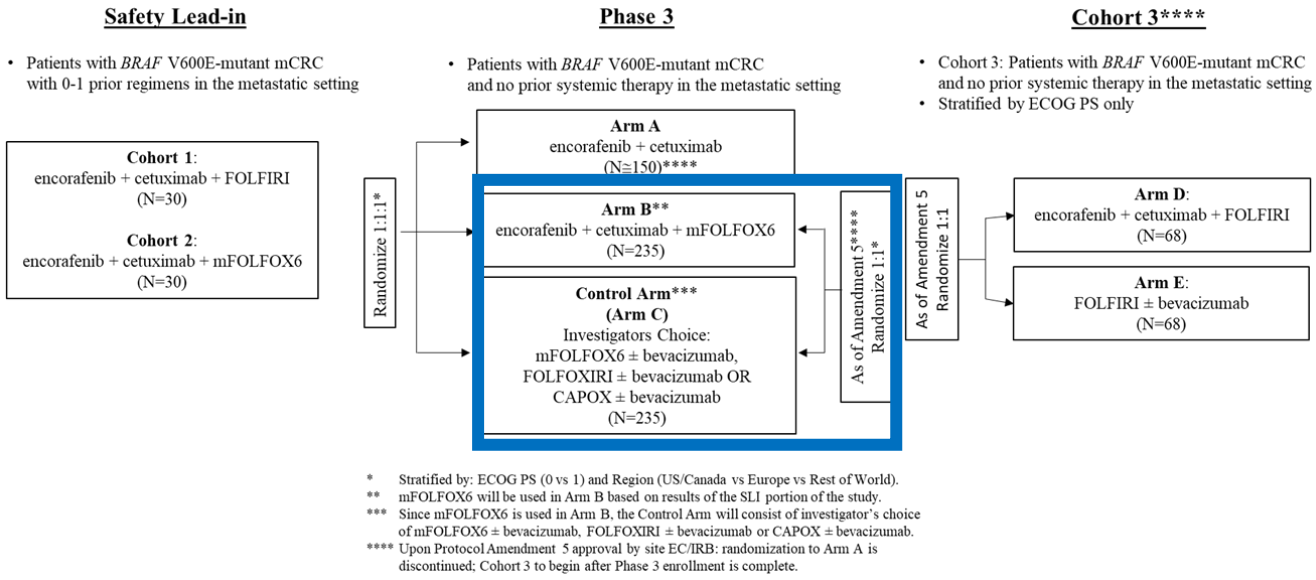
The selection of the chosen dose is mainly based on the efficacy and safety results of the BEACON CRC trial in previously treated BRAF V600E Stage IV unresectable colorectal cancer, which led to the approval of encorafenib and cetuximab in the respective setting.

2.4.2. Main study(ies)

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 1. 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 1 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 1 Treatment Regimens in BREAKWATER, Phase 3 (Study C4221015)

Study Treatments	Dose	Frequency
Phase 3		
EC Arm (Arm A)		
Encorafenib Cetuximab	300 mg (4 × 75 mg) oral capsule 500 mg/m^2 (120-minute IV infusion)[a]	QD Q2W
EC + mFOLFOX6 Arm (Arm B)		
Encorafenib Cetuximab mFOLFOX6	300 mg (4 × 75 mg) oral capsule 500 mg/m^2 (120-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,e] 5-FU 400 mg/m^2 IV bolus, then 5-FU 2400 mg/m^2 continuous IV infusion over 46-48 hours[a]	QD Q2W 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 2 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 (6 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

A total of approximately 620 participants will be randomized, initially in a 1:1:1 ratio, to one of the three treatment arms, and then 1:1 to receive EC + chemotherapy (Arm B) or SOC chemotherapy (Arm C) after the approval of Protocol Amendment 5, with a total of approximately 150 participants for Arm A and 235 participants each for Arm B and Arm C.

Approximately 230 PFS events by BICR will be required to have at least 85% power to detect a hazard ratio of 0.67 using a one-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 assumption of a hazard ratio of 0.67 under the exponential model assumptions with median PFS of 7 months on the control arm and 10.4 months on Arm B. Further assumptions include a drop-out hazard rate of 0.07 for each treatment arm and a non-uniform participants accrual over 26 months (for 2 arms: 6 participants per month for the first 5 months, 11 participants a month for months 6 through 7, 16 participants a month for months 8 through 11, 23 participants a month for months 12 through 16, and 24 participants per month thereafter).

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

For the Phase 3 portion of the study, a randomisation list stratified by ECOG (0 versus 1) and region (US/Canada versus Europe versus Rest of World) was used. This was an open-label study; however, the specific study intervention dispensed to the participant was assigned using an IRT.

Initially participants were randomised at a ratio of 1:1:1 to receive EC, EC + mFOLFOX6, or standard-of-care chemotherapy (Control), and then 1:1 to receive EC + mFOLFOX6 or standard-of-care chemotherapy after the approval of Protocol Amendment 5 (and discontinuation of enrolment of EC Arm).

Blinding (masking)

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

Treatment was 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 3 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.

For the Phase 3 portion of the study a hierarchical testing procedure was to be used to control the family-wise type I error rate as 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 enrollment 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 enrollment 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).
- If the results of PFS by BICR analysis are not statistically significant, but the ORR by BICR on 220 participants resulted statistically significant, an interim analysis for efficacy OS will be conducted at the time of PFS analysis using a portion of nominal 1-sided alpha of 0.001. If the value of the test statistic for interim OS of Arm B versus Arm C at the time of PFS analysis exceeds the efficacy boundary no further test will be performed. If the results of the interim analysis of OS are not statistically significant, a final OS analysis will be performed once 297 events are observed for Arm B + Arm C.

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 4.

Table 4 PFS outcome and Events dates-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 analysed 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 2 Participant Disposition (FAS, Phase 3 DCO 06 Jan 2025)

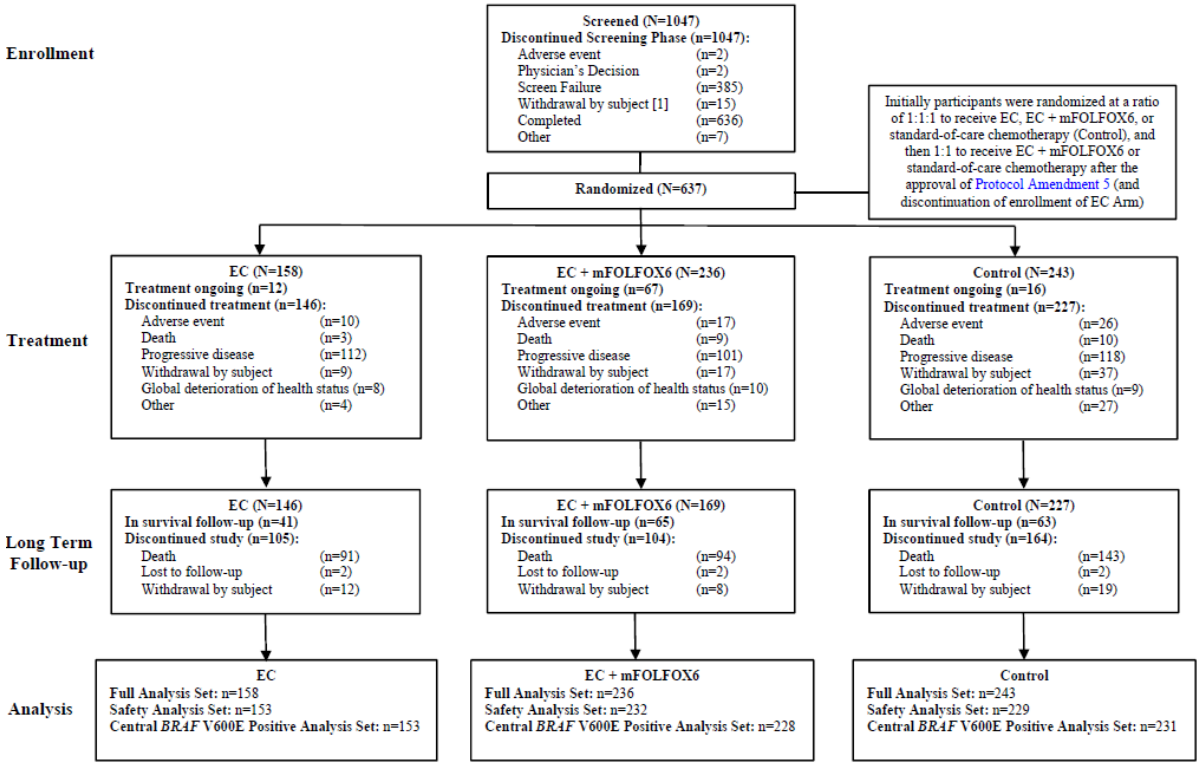


Table 5. Disposition Events Summary - Phase 3 Full Analysis Set (Protocol C4221015)

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)

Table 5. 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 (%)
Withdrawal by subject	12 (7.6)	8 (3.4)	19 (7.8)
Ongoing	41 (25.9)	65 (27.5)	63 (25.9)

Recruitment

Conduct of the study

The study was conducted between 21 December 2020 (FPFV) and 22 December 2023.

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 6 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 7 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	- Incorporated MHRA recommendations into the protocol. - Added specific guidance on management of cancer patients during the COVID-19 pandemic, including risk assessment and mitigation. - Added guidance for administration of study intervention in participants with SARS-CoV-2 infection.
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. - Aligned laboratory assessments and safety monitoring text with other protocol sections and local requirements. - Updated patient-reported outcomes (PRO) instructions and scoring descriptions.

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. - Added country-specific information on testing and destruction of biological samples for participants enrolled in mainland China.

Protocol deviations

Table 8 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 9. 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 10. 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 (%)

Table 10. 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)
BRAF V600E Status, Tumor Tissue (Central), n (%)			

Table 10. 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 (%)
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 11 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

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 12 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

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 adiministered 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 13 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	110 (69.6)	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)

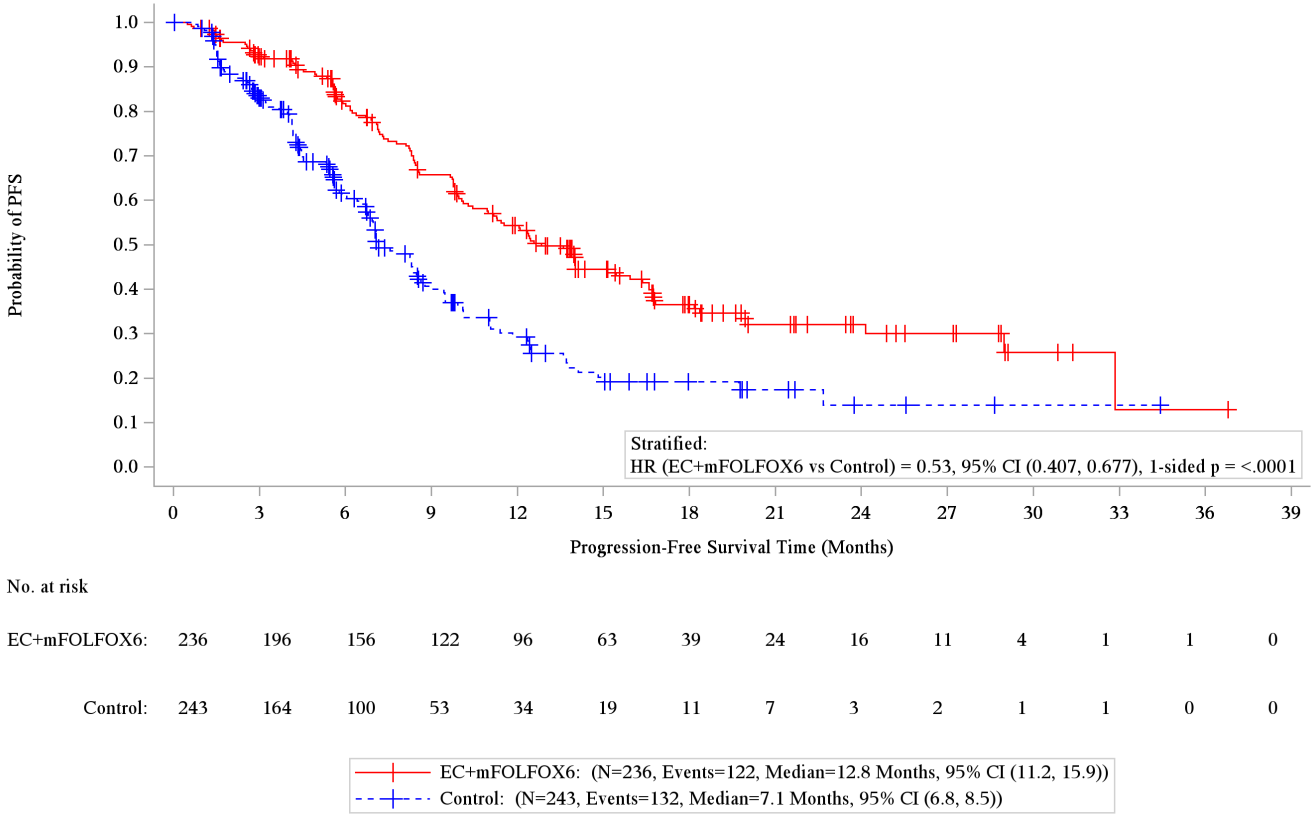
Full Analysis Set: all randomized. Safety Analysis Set: randomized and received ⩾1 dose, summarised by treatment received. Central BRAF V600E Set: BRAF-positive by central lab. ORR Subset: first 110 randomized per arm; totals may exceed 110 if multiple randomizations occurred on the same day. PK Analysis 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 3 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 14 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, 0.606)	0.322 (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 4 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)

Percentages calculated based on N, the number of patients in the full analysis set in each treatment group. Data cutoff date: 06JAN2025

The treatment effect is consistently present in important subgroups, see Figure 4.

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 15 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	3 (1.3)	2 (0.8)
Start of new anti-cancer therapy	38 (16.1)	41 (16.9)
Event after ≥2 missing post-baseline assessments	4 (1.7)	5 (2.1)
Withdrawal of consent	5 (2.1)	15 (6.2)
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 (0.760, 0.875)	0.612 (0.537, 0.678)
at 9 months	0.671 (0.604, 0.729)	0.410 (0.333, 0.487)
at 12 months	0.571 (0.499, 0.636)	0.301 (0.227, 0.378)
at 15 months	0.476 (0.403, 0.548)	0.208 (0.140, 0.285)
at 18 months	0.376 (0.304, 0.485)	0.106 (0.061, 0.157)
at 21 months	0.315 (0.248, 0.389)	0.106 (0.061, 0.157)
Kaplan–Meier Quartiles (95% CI)		
Q1	7.8 (6.7, 9.7)	4.2 (3.9, 4.7)
Median	12.6 (11.2, 16.1)	7.2 (6.8, 8.5)
Q3	25.2 (19.9, NE)	12.3 (10.4, 14.8)
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 16).

Table 16 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 (6 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 17).

Table 17 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	49 (31.0)	144 (61.0)	63 (25.9)
Stable disease	57 (36.1)	51 (21.6)	93 (38.3)
Non-CR/Non-PD	7 (4.4)	3 (1.3)	9 (3.7)
Progressive disease	12 (7.6)	8 (3.4)	20 (8.2)
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)	4 (1.7)	3 (1.2)
No post-baseline assessments due to other reasons	8 (5.1)	9 (3.8)	16 (6.6)
New anti-cancer therapy before first post-baseline assessment	0	1 (0.4)	4 (1.7)
Stable disease too early	0	0	3 (1.2)
Progressive disease too late (>12 weeks after randomization)	0	0	3 (1.2)
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 5 and Table 18.

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

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 favor of EC+mFOLFOX6 compared to Control. p-value based on stratified log-rank test.
Data cutoff date: 06JAN2025

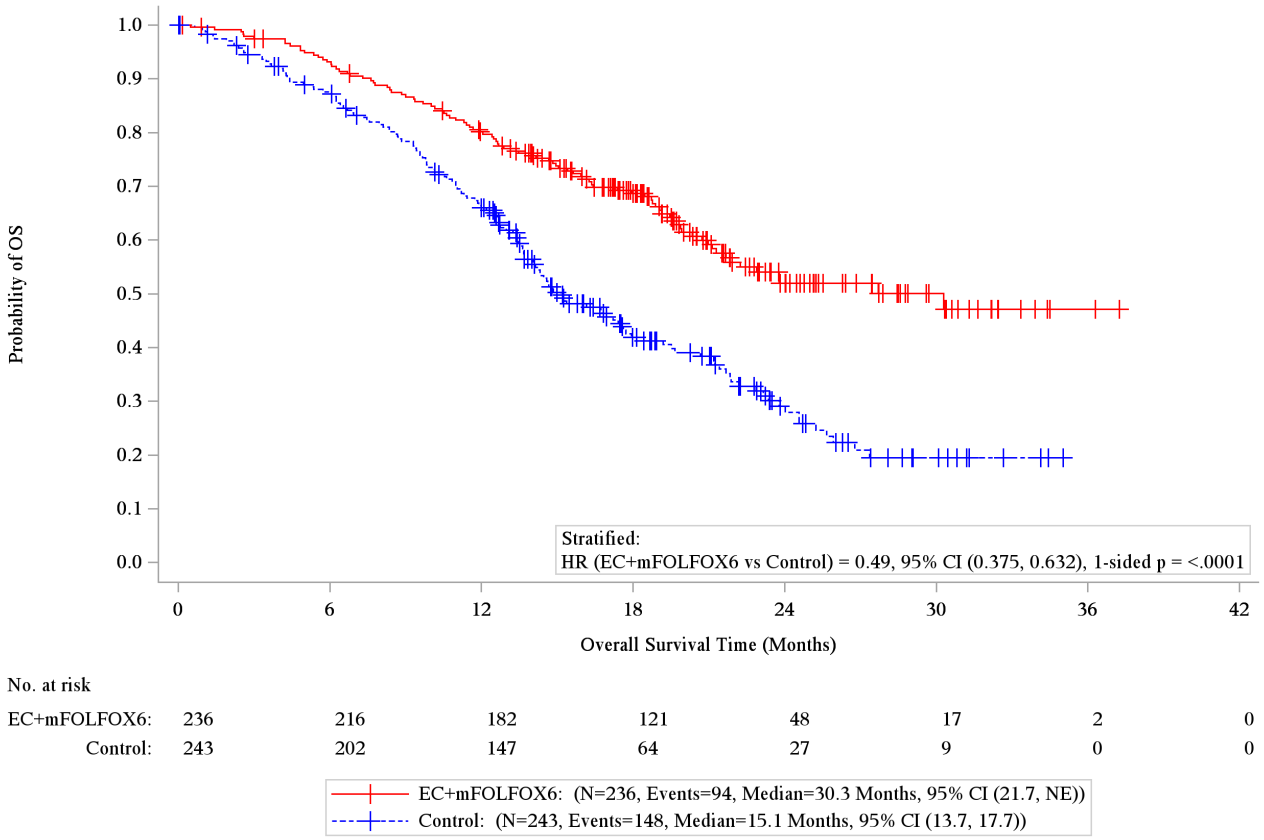


Table 18 Summary of Overall Survival – Phase 3 EC+mFOLFOX6 and Control Arms, Full Analysis Set (Protocol C4221015)

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.

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 19 and Table 20).

Table 19: 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 20: 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 21).

Table 21 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 (0.461, 0.607)	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 22 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
	PFS per BICR	Stratified Hazard Ratio (HR)	0.53
		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).		

2.4.3. 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.

2.4.4. 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.

2.5. Clinical safety

Introduction

The safety profile of cetuximab is well known. The main undesirable effects of cetuximab are skin reactions, which occur in more than 80% of patients, hypomagnesaemia which occurs in more than 10% of patients and infusion-related reactions, which occur with mild to moderate symptoms in more than 10% of patients and with severe symptoms in more than 1% of patients.

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

- 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)
- Cohort 2 – encorafenib + cetuximab (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

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

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/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. 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:
    - EC + mFOLFOX6 arm (N=232) – 11.45 months (i.e 49.8 weeks, range: 1.3 to 161.9 weeks) with 28.4% of participants still receiving study treatment at the time of the data cutoff.
    - Control arm (N=229) – 5.95 months (i.e 25.9 weeks range: 2.0 to 150.0 weeks) with 6.6% of participants still receiving study treatment at the time of the data cutoff.

      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 23 Duration of treatment (study) - Phase 3 Safety Set (Protocol C4221015)

	EC regimen (N=153)	EC+FOLFOX6 (N=232)	Control (N=229)
Duration of treatment (weeks)			
Mean (SD)	39,68 (34,27)	55,45 (35,41)	30,88 (24,83)
Q1	19,1	26,1	13,1
Median (Range)	27,0 (2,0; 153,57)	49,79 (1,29; 161,86)	25,86 (2,00; 150,00)
Q3	47,9	79,5	39,0
Category (weeks)			
< 4	6 (3,9)	3 (1,3)	12 (5,2)
>= 4 - < 12	11 (7,2)	14 (6,0)	38 (16,6)
>= 12 - < 24	42 (27,5)	35 (15,1)	53 (23,1)
>= 24 - < 36	36 (23,5)	29 (12,5)	54 (23,6)
>= 36 - < 48	20 (13,1)	29 (12,5)	29 (12,7)
>= 48 - < 60	9 (5,9)	26 (11,2)	18 (7,9)
>= 60	29 (19,0)	96 (41,4)	25 (10,9)

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%).

Demographic and baseline characteristics

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

Adverse events

An overview of AEs in Phase 3 is provided by treatment arm in Table below.

- All participants in the EC + mFOLFOX6 Arm, and almost all participants in the Control Arm, had at least 1 all-causality AE and at least 1 treatment related AE.
- The overall frequencies of participants with all-causality and treatment related AEs and SAEs, and Grade 5 AEs were generally similar between the EC + mFOLFOX6 Arm and the Control Arm.
- The overall frequencies of participants with all-causality and treatment related Grade 3/4 AEs, and all-causality dose reduction of any study intervention due to AEs and dose interruption of

any study intervention due to AEs were higher (≥10% difference) in the EC + mFOLFOX6 Arm than the Control Arm.

Table 24: Overview of Adverse Events - Phase 3 Safety Set (Protocol C4221015)

Adverse Event Category	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
Number (%) of Participants with AEs (All Causality)			
Any AEs	149 (97.4)	232 (100.0)	227 (99.1)
Any non-serious AEs	147 (96.1)	232 (100.0)	224 (97.8)
Any Serious AEs	46 (30.1)	107 (46.1)	89 (38.9)
AEs with Maximum CTCAE Grade 3 or 4	65 (42.5)	189 (81.5)	153 (66.8)
AEs with Maximum CTCAE Grade 5	4 (2.6)	10 (4.3)	10 (4.4)
Dose reduction of any study intervention due to AE	16 (10.5)	152 (65.5)	124 (54.1)
Dose reduction of encorafenib due to AE	13 (8.5)	59 (25.4)	0 (0.0)
Dose reduction of cetuximab due to AE	4 (2.6)	21 (9.1)	0 (0.0)
Dose reduction of other study intervention[a] due to AE	0 (0.0)	139 (59.9)	124 (54.1)
Dose interruption of any study intervention due to AE	63 (41.2)	212 (91.4)	168 (73.4)
Dose interruption of encorafenib due to AE	61 (39.9)	157 (67.7)	0 (0.0)
Dose interruption of cetuximab due to AE	49 (32.0)	168 (72.4)	0 (0.0)
Dose interruption of other study intervention[a] due to AE	0 (0.0)	196 (84.5)	168 (73.4)
AE leading to discontinuation of any study intervention	20 (13.1)	62 (26.7)	40 (17.5)
Permanent discontinuation of encorafenib due to AE	16 (10.5)	32 (13.8)	0 (0.0)
Permanent discontinuation of cetuximab due to AE	20 (13.1)	34 (14.7)	0 (0.0)
Permanent discontinuation of other study intervention[a] due to AE	0 (0.0)	48 (20.7)	40 (17.5)
Number (%) of Participants with Treatment-related AEs			
Related to Any Study Intervention	136 (88.9)	232 (100.0)	217 (94.8)
Treatment-related AEs with Maximum CTCAE Grade 3 or 4	24 (15.7)	177 (76.3)	134 (58.5)
Treatment-related AEs with Maximum CTCAE Grade 5	0 (0.0)	0 (0.0)	1 (0.4)
AEs related to encorafenib	122 (79.7)	211 (90.9)	0 (0.0)
AEs related to cetuximab	126 (82.4)	211 (90.9)	0 (0.0)
AEs related to other study intervention[a]	0 (0.0)	229 (98.7)	217 (94.8)
Serious AEs related to any study intervention	10 (6.5)	45 (19.4)	50 (21.8)

MedDRA v27.1 coding dictionary applied.
AE must be treatment-emergent to be included in this table.
a. Other study intervention includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab (as appropriate for the treatment group).
Dose reduction of other study intervention is defined as reduction of at least one drug.
Dose interruption of other study intervention is defined as temporary stop of at least one drug or permanent stop of at least one (but not all) drugs.
Permanent discontinuation of other study intervention is defined as permanent stop of all drugs.
(Data cutoff date: 06JAN2025

Table 25: Decreasing Frequency of Treatment Emergent Adverse Events by PT in >= 10% in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=153)	EC+mFOLFOX6 (N=232)	Control (N=229)
Number (%) of Participants: by Preferred Term	n (%)	n (%)	n (%)
With Any Adverse Event	149 (97.4)	232 (100.0)	227 (99.1)
Nausea	31 (20.3)	125 (53.9)	114 (49.8)
Anaemia	32 (20.9)	107 (46.1)	58 (25.3)
Diarrhoea	28 (18.3)	97 (41.8)	115 (50.2)
Decreased appetite	25 (16.3)	87 (37.5)	62 (27.1)
Vomiting	22 (14.4)	84 (36.2)	51 (22.3)
Neutrophil count decreased	2 (1.3)	79 (34.1)	67 (29.3)
Arthralgia	53 (34.6)	73 (31.5)	12 (5.2)
Rash	27 (17.6)	70 (30.2)	9 (3.9)
Asthenia	28 (18.3)	68 (29.3)	34 (14.8)
Pyrexia	26 (17.0)	67 (28.9)	36 (15.7)
Neuropathy peripheral	2 (1.3)	64 (27.6)	54 (23.6)
Constipation	22 (14.4)	63 (27.2)	52 (22.7)
Peripheral sensory neuropathy	3 (2.0)	62 (26.7)	54 (23.6)
Fatigue	33 (21.6)	61 (26.3)	64 (27.9)
Neutropenia	3 (2.0)	56 (24.1)	57 (24.9)
Alopecia	13 (8.5)	53 (22.8)	26 (11.4)
Platelet count decreased	3 (2.0)	53 (22.8)	32 (14.0)
Lipase increased	10 (6.5)	52 (22.4)	27 (11.8)
Abdominal pain	25 (16.3)	47 (20.3)	53 (23.1)
Weight decreased	16 (10.5)	44 (19.0)	22 (9.6)
Dermatitis acneiform	30 (19.6)	43 (18.5)	2 (0.9)
Skin hyperpigmentation	19 (12.4)	43 (18.5)	7 (3.1)
White blood cell count decreased	2 (1.3)	43 (18.5)	32 (14.0)
Epistaxis	9 (5.9)	41 (17.7)	32 (14.0)
Hypokalaemia	10 (6.5)	41 (17.7)	26 (11.4)
Dry skin	23 (15.0)	38 (16.4)	11 (4.8)
Hypomagnesaemia	16 (10.5)	38 (16.4)	11 (4.8)
Myalgia	30 (19.6)	38 (16.4)	9 (3.9)
Palmar-plantar erythrodysaesthesia syndrome	5 (3.3)	37 (15.9)	23 (10.0)
Dysgeusia	8 (5.2)	35 (15.1)	32 (14.0)
Headache	24 (15.7)	35 (15.1)	20 (8.7)
Stomatitis	7 (4.6)	35 (15.1)	33 (14.4)
COVID-19	19 (12.4)	34 (14.7)	28 (12.2)
Mucosal inflammation	6 (3.9)	34 (14.7)	24 (10.5)
Paraesthesia	0	34 (14.7)	19 (8.3)
Pruritus	28 (18.3)	32 (13.8)	7 (3.1)
Thrombocytopenia	2 (1.3)	32 (13.8)	21 (9.2)
Aspartate aminotransferase increased	13 (8.5)	31 (13.4)	33 (14.4)

Number of Participants Evaluable for AEs Number (%) of Participants: by Preferred Term	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
Hypoalbuminaemia	8 (5.2)	30 (12.9)	14 (6.1)
Alanine aminotransferase increased	14 (9.2)	29 (12.5)	28 (12.2)
Insomnia	15 (9.8)	29 (12.5)	17 (7.4)
Neurotoxicity	0	26 (11.2)	19 (8.3)
Abdominal pain upper	16 (10.5)	24 (10.3)	19 (8.3)
Back pain	21 (13.7)	24 (10.3)	16 (7.0)
Cough	11 (7.2)	24 (10.3)	12 (5.2)
Haemorrhoids	4 (2.6)	24 (10.3)	8 (3.5)
Urinary tract infection	16 (10.5)	23 (9.9)	16 (7.0)
Malaise	8 (5.2)	20 (8.6)	23 (10.0)
Melanocytic naevus	21 (13.7)	13 (5.6)	0
Hypertension	3 (2.0)	9 (3.9)	35 (15.3)

MedDRA v27.1 coding dictionary applied.
Preferred terms are sorted in descending frequency of EC+mFOLFOX6 column.
(Data cutoff date : 06JAN2025

Table 26: Summary of Treatment-Emergent Adverse Events with Maximum CTCAE Grade 3 or 4 by PT Reported in >= 2% of Participants in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs Number (%) of Participants: by Preferred Term	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
With Any Adverse Event	65 (42.5)	189 (81.5)	153 (66.8)
Neutrophil count decreased	1 (0.7)	44 (19.0)	39 (17.0)
Lipase increased	5 (3.3)	40 (17.2)	14 (6.1)
Anaemia	10 (6.5)	35 (15.1)	9 (3.9)
Neutropenia	2 (1.3)	35 (15.1)	23 (10.0)
Neuropathy peripheral	0	18 (7.8)	8 (3.5)
Peripheral sensory neuropathy	0	16 (6.9)	8 (3.5)
Neurotoxicity	0	13 (5.6)	0
White blood cell count decreased	0	13 (5.6)	8 (3.5)
Asthenia	1 (0.7)	12 (5.2)	3 (1.3)
Abdominal pain	5 (3.3)	11 (4.7)	3 (1.3)
Intestinal obstruction	7 (4.6)	10 (4.3)	6 (2.6)
Paraesthesia	0	10 (4.3)	4 (1.7)
Vomiting	2 (1.3)	9 (3.9)	5 (2.2)
Nausea	2 (1.3)	7 (3.0)	9 (3.9)
Palmar-plantar erythrodysaesthesia syndrome	0	7 (3.0)	2 (0.9)

Number of Participants Evaluable for AEs Number (%) of Participants: by Preferred Term	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
Arthralgia	1 (0.7)	6 (2.6)	1 (0.4)
Fatigue	2 (1.3)	6 (2.6)	8 (3.5)
Lymphocyte count decreased	0	6 (2.6)	1 (0.4)
Pulmonary embolism	0	6 (2.6)	8 (3.5)
Decreased appetite	1 (0.7)	5 (2.2)	3 (1.3)
Febrile neutropenia	0	5 (2.2)	11 (4.8)
Hypokalaemia	2 (1.3)	5 (2.2)	7 (3.1)
Pyrexia	2 (1.3)	5 (2.2)	1 (0.4)
Stomatitis	0	5 (2.2)	3 (1.3)
Urinary tract infection	6 (3.9)	5 (2.2)	2 (0.9)
Syncope	3 (2.0)	4 (1.7)	3 (1.3)
Alanine aminotransferase increased	1 (0.7)	3 (1.3)	5 (2.2)
Diarrhoea	2 (1.3)	3 (1.3)	11 (4.8)
Hypertension	1 (0.7)	2 (0.9)	10 (4.4)
Hyponatraemia	4 (2.6)	1 (0.4)	3 (1.3)

MedDRA v27.1 coding dictionary applied.
Preferred terms are sorted in descending frequency of EC+mFOLFOX6 column.
Data cutoff date: 06JAN2025

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%.

Serious adverse event/deaths/other significant events

- Deaths

Deaths during the study occurred in 39.7% EC + mFOLFOX6 Arm and 62.0% Control Arm of the Safety Analysis Set.

Deaths ≤28 days after last dose of study treatment were reported for 4.7% EC + mFOLFOX6 Arm and 4.4% Control Arm; most deaths ≤28 days after last dose of study treatment were due to the disease under study.

Deaths ≤28 days after last dose of study treatment due to disease under study occurred in 3.9% EC + mFOLFOX6 Arm and 3.1% Control Arm.

Deaths ≤28 days after last dose of study treatment due to events other than disease under study in the EC + mFOLFOX6 Arm were GI perforation and unknown (0.4%); and in the Control Arm were cardiac arrest, septic shock, and study treatment toxicity (treatment-related Grade 5 AE of sepsis, as per below) (0.4% each).

In the EC + mFOLFOX6 Arm, 1 participant with death ≤28 days after last dose of study treatment was not considered to have a treatment-emergent Grade 5 AE, as subsequent anticancer therapy was initiated prior to death due to disease under study.

All-causality Grade 5 AEs occurred in 4.3% EC + mFOLFOX6 Arm and 4.4% Control Arm.

All-causality Grade 5 AEs in the EC + mFOLFOX6 Arm were disease progression (2.6%), intestinal obstruction (0.9%), and GI perforation and large intestinal perforation (0.4% each); and in the Control Arm were general physical health deterioration (0.9%), and abdominal sepsis, cardiac arrest, disease progression, dyspnoea, large intestinal perforation, pneumonia, respiratory failure, sepsis, and septic shock (0.4% each).

No Grade 5 treatment-related AEs were reported in the EC + mFOLFOX6 Arm. One participant (0.4%) in the Control Arm had a treatment-related Grade 5 AE of sepsis.

Table 27: Summary of Deaths - Phase 3 Safety Set (Protocol C4221015)

	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
Death	**89 (58.2)**	**92 (39.7)**	**142 (62.0)**
Cause of Death			
Disease Under Study	77 (50.3)	76 (32.8)	126 (55.0)
A Variety Of Diseases	0 (0.0)	0 (0.0)	1 (0.4)
Acute Myelocytic Leukemia	1 (0.7)	0 (0.0)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (0.4)
Commit Suicide	1 (0.7)	0 (0.0)	0 (0.0)
Disease Progression	0 (0.0)	1 (0.4)	0 (0.0)
Euthanasia Due To Clinical Progression Of Disease Under Study	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal Perforation	0 (0.0)	1 (0.4)	0 (0.0)
Hepatic Insufficiency, bilateral Deep Vein Thrombosis, Pulmonary Thromboembolism	1 (0.7)	0 (0.0)	0 (0.0)
Immunocheckpoint Inhibitor Associated Myocarditis	1 (0.7)	0 (0.0)	0 (0.0)
Ischemia Cerebrovascular	0 (0.0)	1 (0.4)	0 (0.0)
Palliative Sedation	1 (0.7)	0 (0.0)	0 (0.0)
Post-Covid Pulmonary Fibrosis	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory And Circulatory Failure	0 (0.0)	0 (0.0)	1 (0.4)
Sepsis And Multiorgan Failure	0 (0.0)	1 (0.4)	0 (0.0)

	EC (N=153) n (%)	EC+mFOLFOX6 (N=232) n (%)	Control (N=229) n (%)
Septic Shock	0 (0.0)	0 (0.0)	2 (0.9)
Study Treatment Toxicity	0 (0.0)	0 (0.0)	2 (0.9)
Uncertain Etiology	0 (0.0)	0 (0.0)	1 (0.4)
Unknown	7 (4.6)	10 (4.3)	8 (3.5)
Deaths Within 28 Days After Last Dose of Study Treatment	**5 (3.3)**	**11 (4.7)**	**10 (4.4)**
Cause of Death			
Disease Under Study	5 (3.3)	9 (3.9)	7 (3.1)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal Perforation	0 (0.0)	1 (0.4)	0 (0.0)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.4)
Study Treatment Toxicity	0 (0.0)	0 (0.0)	1 (0.4)
Unknown	0 (0.0)	1 (0.4)	0 (0.0)
Deaths Within 30 Days After First Dose of Study Treatment	**0 (0.0)**	**1 (0.4)**	**3 (1.3)**
Cause of Death			
Disease Under Study	0 (0.0)	1 (0.4)	2 (0.9)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.4)

The denominator to calculate percentages is N, the number of participants in the Safety Analysis Set within each treatment group.
(Data cutoff date: 06JAN2025

- Serious adverse events

All-causality SAEs occurred in 46.1% EC + mFOLFOX6 Arm and 38.9% Control Arm. The most frequent (≥3% of participants) all-causality SAEs by PT in the EC + mFOLFOX6 Arm were intestinal obstruction (4.7%), pyrexia (3.9%), anemia and disease progression (3.4% each); and in the Control Arm were febrile neutropenia (3.9%) and abdominal pain (3.1%).

Table 28: Summary of Serious Treatment-Emergent Adverse Events in ≥1% in in Any Phase 3 Treatment Arm by PT (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=153)	EC+mFOLFOX6 (N=232)	Control (N=229)
Number (%) of Participants: by Preferred Term	**n (%)**	**n (%)**	**n (%)**
With Any Adverse Event	46 (30.1)	107 (46.1)	89 (38.9)
Intestinal obstruction	6 (3.9)	11 (4.7)	5 (2.2)
Pyrexia	0	9 (3.9)	3 (1.3)
Anaemia	0	8 (3.4)	1 (0.4)
Disease progression	4 (2.6)	8 (3.4)	1 (0.4)
Abdominal pain	3 (2.0)	6 (2.6)	7 (3.1)
Vomiting	1 (0.7)	6 (2.6)	1 (0.4)
Sepsis	1 (0.7)	4 (1.7)	1 (0.4)
Alanine aminotransferase increased	0	3 (1.3)	1 (0.4)
Ascites	0	3 (1.3)	0
Ileus	2 (1.3)	3 (1.3)	4 (1.7)

Number of Participants Evaluable for AEs	EC (N=153)	EC+mFOLFOX6 (N=232)	Control (N=229)
Number (%) of Participants: by Preferred Term	**n (%)**	**n (%)**	**n (%)**
Pneumonia	0	3 (1.3)	5 (2.2)
Pulmonary embolism	0	3 (1.3)	1 (0.4)
Small intestinal obstruction	1 (0.7)	3 (1.3)	1 (0.4)
Urinary tract infection	6 (3.9)	3 (1.3)	2 (0.9)
Febrile neutropenia	0	2 (0.9)	9 (3.9)
Acute kidney injury	2 (1.3)	1 (0.4)	3 (1.3)
Diarrhoea	0	1 (0.4)	5 (2.2)
Large intestinal obstruction	0	1 (0.4)	3 (1.3)
Enteritis	0	0	3 (1.3)
Myocardial infarction	2 (1.3)	0	3 (1.3)

MedDRA v27.1 coding dictionary applied.
Preferred terms are sorted in descending frequency of EC+mFOLFOX6 column.
(Data cutoff date: 06JAN2025

Adverse events of special interest

In Phase 3, all-causality encorafenib AESIs occurred in 79.3% EC + mFOLFOX6 Arm and 65.9% Control Arm. The most frequent (≥10% of participants) all-causality encorafenib AESI by grouping in the EC + mFOLFOX6 Arm and the Control Arm was myelosuppression (77.6% and 64.6%, respectively). Other AESIs (cutaneous non-squamous cell carcinoma, hepatic failure, QT prolongation, and facial paresis) were each reported in <7% of participants in each arm and with <5% difference between the EC + mFOLFOX6 Arm and the Control Arm.

Nearly half of all-causality encorafenib AESIs were Grade 1 or 2 in severity in both treatment arms.

All-causality Grade 3 encorafenib AESIs were reported in 35.3% EC + mFOLFOX6 Arm and 26.2% Control Arm; the most frequent (≥5% of participants) by grouping in the EC + mFOLFOX6 Arm and the Control Arm was myelosuppression (33.6% and 25.3%, respectively).

All-causality Grade 4 encorafenib AESIs were reported in 10.8% EC + mFOLFOX6 Arm and 7.9% Control Arm; the most frequent (≥5% of participants) by grouping in the EC + mFOLFOX6 Arm and the Control Arm was myelosuppression (10.8% and 7.9%, respectively).

No all-causality Grade 5 encorafenib AESIs were reported in the EC + mFOLFOX6 Arm. One participant (0.4%) in the Control Arm had a Grade 5 encorafenib AESI of QT prolongation (PT of cardiac arrest considered not treatment-related).

Most AESIs were considered treatment-related; the percentage of participants with treatment-related encorafenib AESIs was 74.6% EC + mFOLFOX6 Arm and 63.3% Control Arm.

The frequency of individual encorafenib AESIs was consistent (<1% difference) between the EC + mFOLFOX6 Arm of Phase 3 and the POOLED population. FACIAL PARESIS was not reported in participants who received EC + mFOLFOX6.

No new safety signals were identified based on assessments of AESIs.

Table 29: CRC - Summary of Clinical Safety Summary of Treatment-Emergent AESIs for Encorafenib, by Grouping Terms in Decreasing Frequency of All Grades (All Grades, Grade 3

or Higher) for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of participants evaluable for AEs	Phase 3 EC (N=153)	Phase 3 EC+mFOLFOX (N=232)	Phase 3 Control (N=229)	SLI EC+ mFOLFOX6 (N=27)	Pooled EC + mFOLFOX6 (N=259)
With any AE Grade ≥3	44 (28,8) 16 (10,5)	184 (79,3) 107 (46,1)	151 (65,9) 79 (34,5)	20 (74,1) 11 (40,79	2024 (78,8) 118 (45,6)
Myelosuppression Grade ≥3	37 (24,2) 13 (8,5)	180 (77,6) 103 (44,4)	148 (64,6) 76 (33,2)	20 (74,1) 11 (40,7)	200 (77,2) 114 (44,0)
QT prolongation Grade ≥3	8 (5,2) 3 (2,0)	16 (6,9) 6 (2,6)	5 (2,2) 5 (2,29	2 (7,4) 2 (7,4)	18 (6,9) 8 (3,1)
Hepatic failure Grade ≥3	1 (0,7) 1 (0,7)	4 (1,7) 0	3 (1,3) 1 (0,4)	0 0	4 (1,5) 0
Cutaneous non-squamous cell carcinoma Grade ≥3	0 0	3 (1,3) 0	1 (0,4) 0	0 0	3 (1,2) 0
Facial paresis Grade ≥3	1 (0,7) 0	0 0	0 0	0 0	0 0

MedDRA v27.1 coding dictionary applied.
Grouping terms are sorted in descending frequency of Any Grade Phase 3 EC+mFOLFOX6 column.
Cut-off Date: BREAKWATER Phase 3 06JAN2025, BREAKWATER SLI 22DEC2023

Table 30: CRC - Summary of Clinical Safety Summary of Serious Treatment-Emergent AESIs for Encorafenib, by Grouping Terms in Decreasing Frequency of All Grades (All Grades, Grade 3 or Higher) for Phase 3, Safety Lead-in and POOLED Set (All Causalities) (Protocol C4221015)

Number of participants evaluable for AEs	Phase 3 EC (N=153)	Phase 3 EC+mFOLFOX (N=232)	Phase 3 Control (N=229)	SLI EC+ mFOLFOX6 (N=27)	Pooled EC + mFOLFOX6 (N=259)
With any AE Grade ≥3	1 (0,7) 1 (0,7)	15 (6,5) 14 (6,0)	13 (5,7) 13 (5,7)	2 (7,4) 2 (7,4)	17 (6,6) 16 (6,2)
Myelosuppression Grade ≥3	0 0	12 (5,2) 12 (5,2)	11 (4,8) 11 (4,8)	1 (3,7) 1 (3,7)	13 (5,0) 13 (5,0)
QT prolongation Grade ≥3	0 0	2 (0,9) 2 (0,9)	1 (0,4) 1 (0,4)	2 (7,4) 2 (7,4)	4 (1,5) 4 (1,5)
Hepatic failure Grade ≥3	1 (0,7) 1 (0,7)	0 0	1 (0,4) 1 (0,4)	0 0	0 0
Cutaneous non-squamous cell carcinoma Grade ≥3	0 0	1 (0,49) 0	0 0	0 0	1 (0,4) 0

MedDRA v27.1 coding dictionary applied.
Grouping terms are sorted in descending frequency of Any Grade Phase 3 EC+mFOLFOX6 column.
Cut-off Date: BREAKWATER Phase 3 06JAN2025, BREAKWATER SLI 22DEC2023

Adverse drug reactions in the target indication

In Phase 3, the most frequent ADRs (≥25% of participants, all grades) by ADR term in the EC + mFOLFOX6 Arm were neuropathy peripheral (69.4%), nausea (53.9%), fatigue (53.4%), diarrhoea (41.8%), decreased appetite (37.5%), vomiting (36.2%), rash (36.2%), haemorrhage (34.1%), arthralgia (32.3%), abdominal pain (31.9%), pyrexia (29.3%), and constipation (27.2%); and in the Control Arm were neuropathy peripheral (58.5%), diarrhoea (50.2%), nausea (49.8%), fatigue (41.0%), abdominal pain (30.6%), and decreased appetite (27.1%).

The most frequent ADRs (≥25% of participants, all grades) by ADR term in the pooled population were neuropathy peripheral (68.3%), nausea (56.0%), fatigue (54.1%), diarrhoea (41.3%), rash (37.1%), vomiting (36.7%), decreased appetite (36.7%), haemorrhage (33.6%), abdominal pain (32.8%), arthralgia (32.0%), pyrexia (31.7%), and constipation (27.0%).

The frequency of individual ADR terms was consistent (<3% difference) between the EC + mFOLFOX6 Arm of Phase 3 and the pooled population.

The ADRs of alopecia, dysgeusia, and neurotoxicity were identified as new with respect to the initial MAA for mCRC. However, alopecia and dysgeusia are known ADRs for encorafenib in combination with binimetinib in other indications and/or as a single agent.

Table 31 Tabulated list of adverse reactions – encorafenib 300 mg in combination with cetuximab and FOLFOX

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)

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

The most frequent chemistry parameter that shifted from Grade ≤2 at baseline to Grade 3 post baseline (≥ 10% of participants) in the EC + mFOLFOX6 Arm and the Control Arm was lipase increased (41.8% and 27.3%, respectively).

The most frequent chemistry parameter that shifted from Grade ≤2 at baseline to Grade 4 post baseline (≥ 5% of participants) in the EC + mFOLFOX6 Arm was lipase increased (11.8%). There were no chemistry parameters that shifted from Grade ≤2 at baseline to Grade 4 post baseline reported in ≥ 5% of participants in the Control Arm; the most frequent (≥ 1% of participants) was lipase increased (1.4%).

Table 32: 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)

N = the number of participants in the safety analysis set with baseline (<= grade 2 or missing) and at least one post-baseline assessment for each parameter in each treatment group.
n = the number of participants with post-baseline meeting criteria (>= grade 3).
Data cutoff date: 06JAN2025

One participant in the EC + mFOLFOX6 Arm met the case finding criteria for a potential Hy's Law case due to ALT or AST ≥3 × ULN & TBILI ≥2 × ULN with a missing ALP value, thus full clinical assessment of this participant's hepatic profile was limited, and no serious clinical hepatic events were reported.

Vital signs

- Blood Pressure

Post-baseline high SBP values (≥160 mmHg and increase from baseline ≥20 mmHg) occurred in 4.8% EC + mFOLFOX6 Arm and 14.9% Control Arm, and post-baseline low SBP values (≤90 mmHg and decrease from baseline ≥20 mmHg) occurred in 10.5% EC + mFOLFOX6 Arm and 0.5% Control Arm.

Post-baseline high DBP values (≥100 mmHg and increase from baseline ≥15 mmHg) occurred in 3.9% EC + mFOLFOX6 Arm and 10.8% Control Arm, and post-baseline low DBP values (≤50 mmHg and decrease from baseline ≥15 mmHg) occurred in 11.4% EC + mFOLFOX6 Arm and 0.9% Control Arm.

- Pulse Rate

Post-baseline abnormal high pulse rate values (≥120 bpm and increase from baseline ≥15 bpm) occurred in 5.2% EC + mFOLFOX6 Arm and 5.4% Control Arm, and post-baseline abnormal low pulse rate values (≤50 bpm and decrease from baseline ≥15 bpm) occurred in 1.7% EC + mFOLFOX6 Arm and 1.4% Control Arm.

Temperature

Post-baseline high temperature values (≥37.5° C) occurred in 10.0% EC + mFOLFOX6 Arm and 7.2% Control Arm, and post-baseline low temperature values (≤36° C) occurred in 60.4% EC + mFOLFOX6 Arm and 51.4% Control Arm.

- ECGs

New QTcF > 500 ms occurred in 4.0% EC + mFOLFOX6 Arm and 0.9% Control Arm. An increase from baseline in QTcF of >60 msec occurred in 11.9% EC + mFOLFOX6 Arm and 3.2% Control Arm.

No clinically meaningful findings in the vital signs measurements or other observations related to safety were observed in this study. The assessments and observations in ECGs were as expected.

Safety in special populations

Table 33: Safety in Special Groups and Populations

Intrinsic Factors (age, sex, 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.
Extrinsic Factors	- As of this MAA, no new information has been generated regarding extrinsic factor data for encorafenib and cetuximab.
Hepatic Impairment	- There is no new information on hepatic impairment.
Renal Impairment	- There is no new information on renal impairment.
Paediatrics	- As of this MAA, the safety and effectiveness of encorafenib and cetuximab has not been established in pediatric patients.
Pregnancy and Lactation	- As of this MAA, no new information has been generated regarding the use of encorafenib and cetuximab in pregnancy and lactation.
Overdose	- As of this MAA, no new information has been generated regarding overdose of encorafenib and cetuximab.
Drug Abuse	- As of this MAA, no new information has been generated regarding abuse potential of encorafenib and cetuximab.
Withdrawal and rebound	- No new information about withdrawal and rebound of encorafenib and cetuximab has been generated. No studies have been conducted to assess withdrawal and rebound effects.
Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability	- No new information about the effects on the ability to drive or operate machinery or impairment of mental ability has been generated. No studies have been performed on the effects of encorafenib or cetuximab on the ability to drive or operate machinery.

Safety related to drug-drug interactions and other interactions

As of this MAA, no new dedicated clinical pharmacology studies have been completed.

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

Discontinuation due to adverse events

Discontinuation of Any Study Intervention

All-causality AEs associated with permanent discontinuation of any study intervention occurred in 26.7% EC + mFOLFOX6 Arm and 17.5% Control Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were asthenia (3.0%), anemia (2.6%), lipase increased (2.2%), decreased appetite, disease progression, hypersensitivity, infusion related reaction, nausea, peripheral sensory neuropathy, platelet count decreased, and urinary tract infection (1.3% each); and in the Control Arm were intestinal obstruction (2.2%) and general physical health deterioration (1.3%).

- Discontinuation of Encorafenib

All-causality AEs associated with permanent discontinuation of encorafenib occurred in 13.8% EC + mFOLFOX6 Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were lipase increased (2.2%) and disease progression (1.3%).

- Discontinuation of Cetuximab

All-causality AEs associated with permanent discontinuation of cetuximab occurred in 14.7% EC + mFOLFOX6 Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were lipase increased (2.2%), disease progression, and infusion related reaction (1.3% each).

- Discontinuation of Other Intervention

All-causality AEs associated with permanent discontinuation of other study intervention occurred in 20.7% EC + mFOLFOX6 Arm and 17.5% Control Arm; the most frequent (≥1% of participants) in the EC + mFOLFOX6 Arm were asthenia (2.6%), anemia (2.2%), decreased appetite, disease progression, peripheral sensory neuropathy, platelet count decreased, and urinary tract infection (1.3% each); and in the Control Arm were intestinal obstruction (2.2%) and general physical health deterioration (1.3%).

Table 34 Summary of TEAE Associated with Permanent Discontinuation of Any Study Intervention by PT and Maximum CTCAE Grade in >= 1% in Any Phase 3 Treatment Arm (All Causalities) - Phase 3 Safety Set (Protocol C4221015)

Number of Participants Evaluable for AEs	EC (N=153)		EC+mFOLFOX6 (N=232)		Control (N=229)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants: **by Preferred Term**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With Any Adverse Event	**20 (13.1)**	**16 (10.5)**	**62 (26.7)**	**36 (15.5)**	**40 (17.5)**	**36 (15.7)**
Asthenia	0	0	7 (3.0)	2 (0.9)	1 (0.4)	0
Anaemia	0	0	6 (2.6)	5 (2.2)	0	0
Lipase increased	0	0	5 (2.2)	2 (0.9)	1 (0.4)	1 (0.4)
Decreased appetite	0	0	3 (1.3)	2 (0.9)	0	0
Disease progression	3 (2.0)	3 (2.0)	3 (1.3)	3 (1.3)	1 (0.4)	1 (0.4)
Hypersensitivity	0	0	3 (1.3)	2 (0.9)	0	0
Infusion related reaction	3 (2.0)	2 (1.3)	3 (1.3)	2 (0.9)	0	0
Nausea	0	0	3 (1.3)	0	1 (0.4)	1 (0.4)
Peripheral sensory neuropathy	0	0	3 (1.3)	1 (0.4)	0	0
Platelet count decreased	0	0	3 (1.3)	0	1 (0.4)	0

Number of Participants Evaluable for AEs	EC (N=153)		EC+mFOLFOX6 (N=232)		Control (N=229)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Number (%) of Participants:	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
by Preferred Term						
Urinary tract infection	0	0	3 (1.3)	0	1 (0.4)	1 (0.4)
Intestinal obstruction	2 (1.3)	2 (1.3)	2 (0.9)	2 (0.9)	5 (2.2)	4 (1.7)
General physical health deterioration	1 (0.7)	0	0	0	3 (1.3)	2 (0.9)

MedDRA v27.1 coding dictionary applied.
Preferred terms are sorted in descending frequency of Any Grade EC+mFOLFOX6 column.
Other study intervention includes: irinotecan, oxaliplatin, leucovorin or levo-leucovorin, fluorouracil (bolus or infusion), capecitabine, and bevacizumab (as appropriate for the treatment group).
Permanent discontinuation of other study intervention is defined as permanent stop of all drugs.
Permanent discontinuation of any study intervention is defined as a permanent stop of encorafenib, cetuximab, or other study intervention.
Data cutoff date: 06JAN2025

Dose Reductions Associated with Adverse Events

- Dose Reduction of Any Study Intervention

All-causality AEs associated with dose reduction of any study intervention occurred in 65.5% EC + mFOLFOX6 Arm and 54.1% Control Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (12.1%), neutropenia (10.3%), neuropathy peripheral (7.3%), peripheral sensory neuropathy (6.0%), platelet count decreased (5.6%), and anemia, asthenia, and neurotoxicity (5.2% each); and in the Control Arm were neutropenia (11.4%), neutrophil count decreased (10.9%), peripheral sensory neuropathy (7.4%), neuropathy peripheral (6.6%), and diarrhoea (6.1%).

- Dose Reduction of Encorafenib

All-causality AEs associated with dose reduction of encorafenib occurred in 25.4% EC + mFOLFOX6 Arm; the most frequent (≥2% of participants) were anemia, arthralgia, and lipase increased (2.6% each), and nausea, neurotoxicity, and vomiting (2.2% each).

- Dose Reduction of Cetuximab

All-causality AEs associated with dose reduction of cetuximab occurred in 9.1% EC + mFOLFOX6 Arm; the most frequent (≥2% of participants) in the EC + mFOLFOX6 Arm was weight decreased (2.6%).

- Dose Reduction of Other Intervention

All-causality AEs associated with dose reduction of other study intervention occurred in 59.9% EC + mFOLFOX6 Arm and 54.1% Control Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (11.6%), neutropenia (9.9%), neuropathy peripheral (7.3%), peripheral sensory neuropathy (6.0%), platelet count decreased (5.6%), and asthenia (5.2%); and in the Control Arm were neutropenia (11.4%), neutrophil count decreased (10.9%), peripheral sensory neuropathy (7.4%), neuropathy peripheral (6.6%), and diarrhoea (6.1%).

Dose Interruptions Associated with Adverse Events

- Dose Interruption of Any Study Intervention

All-causality AEs associated with dose interruption of any study intervention occurred in 91.4% EC + mFOLFOX6 Arm and 73.4% Control Arm; the most frequent (≥10% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (19.4%), neutropenia (16.4%), pyrexia (15.1%), neuropathy peripheral (12.1%), anemia (11.6%), and COVID-19 and peripheral sensory neuropathy (11.2% each); and in the Control Arm were neutrophil count decreased (13.1%) and neutropenia (11.4%).

- Dose Interruption of Encorafenib

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

- Dose Interruption of Cetuximab

All-causality AEs associated with dose interruption of cetuximab occurred in 72.4% EC + mFOLFOX6 Arm; the most frequent (≥5% of participants) in the EC + mFOLFOX6 Arm were neutrophil count decreased (15.1%), neutropenia (12.9%), anemia (9.9%), COVID-19 (9.1%), pyrexia (8.6%), platelet count decreased (7.8%), and thrombocytopenia (5.6%).

- Dose Interruption of Other Intervention

All-causality AEs associated with dose interruption of other study intervention occurred in 84.5% EC + mFOLFOX6 Arm and 73.4% Control Arm; the most frequent (≥10% of participants) 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%); and in the Control Arm were neutrophil count decreased (13.1%) and neutropenia (11.4%).

Post marketing experience

Post-marketing experience has been obtained with the EC combination in BRAF V600E-mutant mCRC.

The overall safety data from the EC combination originating from postmarketing sources in the CRC setting were consistent with the known safety profile of encorafenib and cetuximab. No new safety information or unusual trends were identified from postmarketing sources.

2.5.1. 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.

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 frequent (≥20% of participants) treatment-related AEs by PT in the EC + mFOLFOX6 Arm were nausea (50.0%), anemia (33.6%), neutrophil count decreased and vomiting (33.2% each), decreased appetite (32.3%), diarrhoea and rash (27.6% each), neuropathy peripheral and peripheral sensory neuropathy (26.7% each), fatigue (24.1%), asthenia and neutropenia (23.7% each), alopecia (22.8%), platelet count decreased (22.4%), and arthralgia (20.3%); and in the Control Arm were nausea (46.7%), diarrhoea (45.9%), neutrophil count decreased (29.3%), fatigue (24.9%), neutropenia (24.5%), peripheral sensory neuropathy (23.6%), neuropathy peripheral (23.1%), and decreased appetite (20.5%)

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 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 cetuximab, the following <u>new ADRs</u> were reported for EC+mFOLFOX6:

Neuropathy peripheral, fatigue, arthralgia, pyrexia, constipation – listed in the SmPC of Braftovi for encorafenib monotherapy, abdominal pain, haemorrhage – for combination of encorafenib and cetuximab; anaemia, thrombocytopenia, neutropenia and infection – are common for FOLFOX regimen.

Of notice, some toxicities were 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 either due to the addition of mFOLFOX6 or due to a longer exposure to EC in BREAKWATER as compared to BEACON CRC.

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.

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.

Altogether the toxicities increased in frequency in EC + FOLFOX as compared to EC, may be due to the addition of FOLFOX. However, the toxicities of EC + FOLFOX 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.

Overall, the combination of EC + FOLFOX presents a safety profile in-line with the known safety profiles of cetuximab in combination with encorafenib (EC) or of FOLFOX although with increased frequency of some toxicities shared by EC and FOLFOX, but with no new safety concern being identified.

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.

2.5.2. 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 Study BREAKWATER (EC-mFOLFOX6-P).

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.

2.5.3. 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.

2.6. Risk management plan

The MAH submitted an RMP version with this application.

Table 35: Changes introduced

Part I	Product(s) Overview	Proposed indication(s) in the EEA has been updated with the indication: for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer in combination with encorafenib and mFOLFOX6, and in combination with encorafenib in patients who have

		received prior systemic therapy. Proposed dosage in the EEA has been updated accordingly.
Part II	Module SI Epidemiology of the Indication(s) and Target Population(s) Module SIII Clinical Trial Exposure Module SV Post Authorization Experience Module SVII Identified and Potential Risks	Updated to latest information and aligned with PBRER with reporting period 01 Oct 2024 to 30 Sep 2025 (including exposure data [both clinical and post-authorization] and details of safety concerns [frequency and number of cases]). Added "Hypophosphatemia" to the list of "Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP".

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

The PRAC considered that the risk management plan version 21.1 is acceptable.

Safety concerns

Table 36: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Not applicable
Important potential risks	(Acute) renal failure Gastrointestinal (GI) perforation
Missing information	Not applicable

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 37: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
(Acute) renal failure	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures: None proposed	Routine pharmacovigilance, including close monitoring
Gastrointestinal (GI) perforation	Routine risk minimization measures: No risk minimization activities are needed at this stage Additional risk minimization measures:	Routine pharmacovigilance, including close monitoring

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None proposed	

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being 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.

2.7.1. 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

Erbitux is indicated for the treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer

- in combination with encorafenib and FOLFOX for the first line treatment.

For details, see section 5.1. 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 colorectal cancer (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 38: Effects Table for Erbitux in combination with encorafenib and mFOLFOX6 for the 1st line treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer (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 (0.407; 0.677) p<0.0001
Unfavourable Effects					

Effect	Short description	Unit	Treatment (95% CI)	Control (95% CI)	Odds ratio/ Hazard ratio (95% CI)
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 cetuximab in combination with encorafenib 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 Erbitux 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.6.a	C.6.a) Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include in combination with encorafenib and FOLFOX treatment of metastatic colorectal cancer with a BRAF V600E mutation for ERBITUX, based on interim results from study C4221015 (BREAKWATER); this is an open-label, multicenter, 3-arm, randomized phase 3 study of 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, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.1 of the RMP has also been submitted.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, 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, 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.