An Open-label, Multicenter, Randomized Phase 3 Study of First line Encorafenib Plus Cetuximab With or Without Chemotherapy Agents 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

Published: 08-10-2020
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This study has been transitioned to CTIS with ID 2023-509405-77-00 check the CTIS register for the current data. The purpose of this Safety Lead In study is to explore if encorafenib and cetuximab in combination with a chemotherapy regimen (either...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54332

Source
ToetsingOnline

Brief title
BREAKWATER

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
BRAF V600E-mutant mCRC, Colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BRAF V600E-mutant mCRC, Colorectal cancer

Outcome measures

Primary outcome

Primary Objectives Safety Lead-In:

- To determine the safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI

Primary Objectives Phase 3:

- To compare the efficacy of EC + mFOLFOX6 (Arm B) vs SOC (Control Arm [Arm C])

as measured by PFS and by ORR

Primary Objectives Cohort 3:

- To compare the efficacy of EC + FOLFIRI (Arm D) vs FOLFIRI with or without

bevacizumab (Control Arm [Arm E]) as measured by ORR

Secondary outcome

Secondary Objectives Safety Lead-In:

- Assess the overall safety and tolerability of EC + mFOLFOX6 and EC + FOLFIRI

- Estimate the efficacy of EC + mFOLFOX6 and EC + FOLFIRI

- Estimate the efficacy of EC + mFOLFOX6 and EC + FOLFIRI

- Characterize the PK of encorafenib, irinotecan, oxaliplatin and relevant metabolite

- Assess drug-drug interaction of encorafenib with irinotecan or oxaliplatin

Secondary Objectives Phase 3:

- Further compare the efficacy of Arm B vs the Control Arm as measured by OS

- Further evaluate efficacy of Arm B vs the Control Arm as measured by ORR, DOR, PFS, PFS2 and TTR

- Evaluate efficacy of EC (Arm A) vs the Control Arm as measured by ORR, DOR, PFS, PFS2 TTR, and OS

- Evaluate efficacy of Arm A vs Arm B as measured by OS, PFS, PFS2, ORR, DOR and TTR

- Determine the safety and tolerability of EC

- Determine the safety and tolerability of EC + mFOLFOX6

Secondary Objectives Cohort 3:

- Further compare the efficacy of Arm D vs Arm E as measured by PFS

Study description

Background summary

Encorafenib and cetuximab in combination have been approved by health authorities (e.g. the US FDA) for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, after prior treatments, but not for patients who have received no prior treatments.

Chemotherapy with mFOLFOX6 and FOLFIRI is a standard treatment for metastatic colorectal cancer. By giving encorafenib and cetuximab with mFOLFOX6 or FOLFIRI, researchers want to see if the study drugs work better as a combination. Your study doctor or study team will let you know which combination you will receive.

Study objective

This study has been transitioned to CTIS with ID 2023-509405-77-00 check the CTIS register for the current data.

The purpose of this Safety Lead In study is to explore if encorafenib and cetuximab in combination with a chemotherapy regimen (either mFOLFOX6 or FOLFIRI) are safe and have beneficial effects on you and your colorectal cancer. This is a small preliminary study to identify the most tolerable combination before the main study. Your study doctor will let you know what combination you are assigned to if you are eligible for this study.

The purpose of the main study, following this Safety Lead In study, is to learn about the effects of the study drugs, encorafenib and cetuximab in combination with chemotherapy regimens, called mFOLFOX6 or FOLFIRI, for the treatment of BRAF V600E-mutant metastatic colorectal cancer. These study drugs are investigational drugs because they are not approved in combination for use in the Netherlands as the first treatment for BRAF V600E-mutant metastatic colorectal cancer.

Study design

This is an open-label, randomised study with a Safety Lead-in followed by the Phase 3 part of the study. The primary purpose is treatment and intervention will be done using a parallel model.

Participants will be eligible for the study based on identification of a BRAF V600E mutation in the tumor as determined by the central laboratory as part of the Molecular Prescreening for the trial or by a local assay result of the tumor or blood obtained any time prior to Screening.

Since the EC regimen has not previously been combined with cytotoxic chemotherapy, the study includes a SLI, to be conducted at a limited number of sites, to evaluate the safety/tolerability and PK of EC in combination with each of the SOC first-line mCRC regimens mFOLFOX6 and FOLFIRI in up to 30 patients per cohort. Participants will be assigned on a rolling basis to receive EC + mFOLFOX6 or FOLFIRI each dosed at their full labeled doses. Sequential patients will be assigned to each cohort in an alternative manner when possible based on eligibility criteria.

Once the SLI is completed, subsequent eligible participants will be randomized 1:1:1 to receive EC (Arm A), EC + mFOLFOX6 or FOLFIRI as determined in the SLI (Arm B), or physician*s choice of SOC regimens typically used in the first-line mCRC setting, including mFOLFOX6, FOLFIRI, infusional fluorouracil/leucovorin/oxaliplatin/ irinotecan (FOLFOXIRI), or capecitabine/oxaliplatin (CAPOX) with or without bevacizumab (or an approved biosimilar; Control Arm).
Participants will be stratified based on ECOG performance status (0 vs. 1) and region (US/Canada vs. the European Economic Area (EEA, which for purposes of this study includes UK) vs. Rest of World). The E-DMC will review the available safety data from all 3 treatment arms after the first 30 patients have been randomized and treated for at least 1 cycle and then approximately every 6 months during the Phase 3 portion of the study.

Intervention

Intervention according to a parallel model. Participants will be assigned to one of two treatment groups:

Group 1:
Encorafenib 4 oral capsules daily.
Cetuximab via IV infusion every 2 weeks.
mFOLFOX6 via IV infusion every 2 weeks.

Group 2:
Encorafenib 4 oral capsules daily.
Cetuximab via IV infusion every 2 weeks.
FOLFIRI via IV infusion every 2 weeks.

Study burden and risks

Burden:
If no archival sample of the patient's tumor material is available, a biopsy of the tumor tissue will be taken at the pre-screening visit to determine if the patient can start the screening process (test for BRAF V600E mutation).
Many of the screening tests and procedures are part of regular cancer care and may be done even if the patient does not join the study. If the patient has had

some of them recently, they may not need to be repeated.
The patient burden includes keeping a dosing diary, physical examinations (measuring height, weight, blood pressure, respiratory rate, heart rate, temperature and a skin exam), blood draws, providing urine samples, ECGs, CT- and/or MRI scans, tumor biopsies, capsules to be taken by mouth, IV-injections and infusions (per infusion 120 minutes for Cetuximab, 46-48 hours for 5-FU and depending on the treatment group 120 minutes for Oxaliplatine and Leucovorine or 90 minutes for Irinotecan and 120 minutes for Leucovorine.

In the first cycle patients have to visit the hospital 4 times, in the following cycles 2 times.

Potential risks in addition to those in question E9 (patients are informed about these risks):
Encorafenib has effects on male reproductive organs. The effect of encorafenib in pregnant women and women who are breastfeeding is not known.

All drugs have a potential risk of causing an allergic reaction, which (if not treated quickly) could become life-threatening. Other allergic reactions may include rash, hives or blisters.

Blood collections may cause pain or bruising. Per cycle 199-245 mL blood will be collected depending on which group the patient is in.

Radiation burden:
With the imaging tests: X-rays and CT scans, we use X-ray radiation. The radiation burden in this study is 10 mSv per scan. The radiation used during the study may cause damage to the patient's health. This risk, however, is small.

Encorafenib Risks
Common (may affect up to 1 in 100 people):
• Abdominal pain
• Change in how food tastes or change in ability to taste
• Constipation
• Feeling that you are dizzily turning around
• High blood sugar
• Increase in blood test results that check how well the liver is working
• Increase in a blood test result that check how well your kidneys are working
• Low red blood cell count
• Muscle weakness and spasms
• New skin growths, including skin cancer
• Skin tags, new moles on the skin or changes in existing moles
• Weakness of facial muscles or loss of facial movement

Uncommon (may affect up to 1 in 1000 people):
• Inflammation of the eye causing discomfort, redness and sensitivity to light

• Inflammation (swelling) of the pancreas causing pain in the abdomen that may also be felt in the back and may be associated with nausea or vomiting. The symptoms can be mild and may go away without treatment, but in some cases can be more severe, needing treatment.

Changes in the electrical activity of the heart, called QT prolongation, has been reported in some people treated with encorafenib. QT prolongation can cause irregular heartbeats that can be life-threatening. Associated symptoms might include shortness of breath, fast or slow heartbeat, and lightheadedness or fainting.

Cetuximab Risks
Common side effects (may affect more than 1 in 100 people):
• Headache
• Tiredness
• Irritation and redness of the eye
• Diarrhea
• Too much water loss which may be due to diarrhea or reduced fluid intake
• Feeling sick or queasy
• Vomiting
• Lack or loss of appetite for food
• Decrease in blood levels of calcium
• Severe infusion-related reactions, in some cases with fatal outcome

Uncommon side effects (may affect more than 1 in 1000 people):
• Blood clots in the veins of the legs
• Blood clots in the lungs
• Inflammation of the eye lid or the front part of the eye
• Inflammation of the lungs (called interstitial lung disease)

Very rare side effects (may affect up to 1 in 10,000 people):
• Blistering or peeling the skin, which may indicate a severe skin reaction called *Stevens-Johnson Syndrome*. If you experience these symptoms, please speak to your doctor immediately.

Not known (cannot be estimated from the available data):
• Skin reactions may lead to super infections and sepsis which may lead to death in rare cases
• Inflammation of the lining of the brain

More specific descriptions of the adverse events can be found in the cetuximab prescribing information for the Netherlands.

Irinotecan Risks
Common side effects (may more than 1 in 100 people):
• Too much water loss which may be due to diarrhea or reduced fluid intake

• Fever with decreased white blood cells
• Infection
• Decreased platelets
• Constipation
• Increased blood levels of creatinine
• Increased blood levels of bilirubin
• Increase in blood levels of certain liver enzymes

Oxaliplatin Risks
Common side effects (may affect more than 1 in 100 people):
• Runny or stuffy nose
• Upper respiratory tract infection
• inflammatory response to infection
• Fever with low white blood cells
• Too much water loss which may be due to diarrhea or reduced fluid intake
• Decreased levels of blood calcium
• Depression
• Insomnia
• Dizziness
• muscle weakness
• Neck stiffness caused by inflammation
• Redness of the eye
• Visual disturbance
• Bleeding
• Flushing
• Blood clots in the veins of the legs
• High blood pressure
• Hiccups
• Blood clots in the lings
• Indigestion
• Gastroesophageal reflux
• Gastrointestinal bleeding
• Rectal bleeding
• Hand & Foot syndrome that causes redness swelling and pain in the palms of the hands or soles of the feet)
• Redness of the skin
• Rash
• Excessive sweating
• Nail disorder
• Joint pain
• Bone pain
• Blood in the urine
• Pain during urination
• Abnormal urination frequency
• Increased levels of blood creatinine
• Weight decrease (metastatic setting)
• Unsteadiness leading to falls

Uncommon side effects (may affect more than 1 in 1000 people):
• Infection causing your immune system to attack your body
• Electrolyte disorder
• Nervousness
• Damage to the inner ear
• Obstruction or blockage in the bowel due to loss of bowel motion that may be associated with abdominal pain, bloating and nausea and vomiting
• Bowel blockage

In very rare cases (may affect up to 1 in 10,000 people), you may experience:
• Decreased platelets due to an allergic reaction
• Red cells not functioning properly
• Motor speech disorder
• Reversible swelling in the brain
• Reversible changes in the eye and vision
• Deafness
• Inflammation of the lungs (called Interstitial lung disease)
• Thickening of the lung tissue
• Inflammation of the inner lining of the colon
• Inflammation of the pancreas

Not known (cannot be estimated from the available data):
• Inflammation of the esophagus
• Changes in the electrical activity of the heart, called QT prolongation that can cause irregular heartbeats which can be life-threatening. Associated symptoms might include shortness of breath, fast or slow heartbeat, and lightheadedness or fainting.

Side Effects of 5-FU
Common side effects (may affect more than 1 in 100 people):
• Fever with low white blood cells
• Angina pectoris-like chest pain

Uncommon side effects (may affect more than 1 in 1000 people):
• Euphoria
• Incidences of excessive tearing, blocked tear ducts
• Visual changes

Contacts

Public
Pfizer

Hudson Boulevard East 66

New York NY 10001
US
Scientific
Pfizer

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New York NY 10001
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Molecular Prescreening Inclusion Criteria
1. For the Safety Lead In (SLI): Male or female participants age >=18 years at the time of informed consent. For Phase 3 and Cohort 3: Male or female participants age >=16 years at the time of informed consent/assent. Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.
2. Body weight >=40 kg.
3. Participants with histologically or cytologically confirmed colorectal adenocarcinoma.
4. Participants with evidence of Stage IV metastatic disease.
Note: Patients with oligometastatic disease previously treated with curative intent are eligible to participate in the study as long as they have baseline measurable disease per RECIST 1.1 Oligometastatic colorectal cancer is characterized by a limited metastatic spread of disease. Oligometastatic disease is defined as the involvement of up to 3 sites with 5 or sometimes more metastases that for their anatomic localization is amenable to local therapies, thus rendering the patient free of disease.
5. Able to provide a sufficient amount of representative tumor specimen for

central testing of BRAF V600E mutation status and tumor tissue assessment.
Note: Tumor sample can be archival or de novo (newly collected fixed biopsy sample) and must be in an FFPE block, or provide a minimum of 15 unstained slides of analyzable tissue. This tissue specimen should be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment. Participants with fewer than the required number of slides with analyzable tissue may be considered eligible if the Sponsor determines that the slides are sufficient for central testing.
6. Capable of giving signed informed consent/assent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Screening Inclusion Criteria
7. Participants who have met all Molecular Prescreening inclusion criteria.
8. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
9. Presence of a BRAF V600E mutation in tumor tissue or blood (e.g., ctDNA genetic testing). The following are acceptable:
a. Local laboratory assay (PCR or NGS-based only) performed at any time prior to Screening using either tumor tissue or blood.
b. Central laboratory assay performed during the Screening period using tumor tissue alone (not blood).
Note: For participants enrolled on the basis of a local BRAF mutation assay, tumor samples must be submitted to the central laboratory for BRAF testing as soon as possible following signing of the ICD. The BRAF status must be confirmed no later than 30 days following first dose of study intervention.
10. The Investigator must obtain prior to Cycle 1 Day 1 (SLI) or date of randomization (Phase 3 and Cohort 3) adequate tumor tissue (primary or metastatic, archival or newly obtained) for submission to a central laboratory for confirmation of BRAF V600E and tumor tissue assessment.
Note: Once BRAF V600E mutation status is determined by the central laboratory (tumor tissue), the results will be considered definitive for eligibility. No repeat testing will be performed.
Note: Lack of BRAF V600E confirmation by the central laboratory may be due to discordance between the local assay and central laboratory results (potential false positive local assay results), or due to inadequate or poor sample condition for central testing (indeterminate results). If at any time in the study there is lack of BRAF V600E confirmation in a total of 6% of the total planned enrollment of the randomized portion of the trial (42 participants) or a discordance between the local assay and the central laboratory of 3% of the total planned enrollment (21 participants), all subsequent participants will be required to have BRAF V600E determined by the central laboratory for treatment (ie, local BRAF testing will no longer be accepted for trial eligibility).
Note: Participants whose sample is determined to be inadequate or who have an indeterminate result on central testing may have additional tumor samples submitted for testing.

For a full list please see section 5.1 of the protocol.

Exclusion criteria

Molecular Prescreening Exclusion Criteria
1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. Presence of acute or chronic pancreatitis.
3. Leptomeningeal disease.
4. History of chronic inflammatory bowel disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) <=12 months prior to randomization.
5. Known DPD deficiency; refer to local fluorouracil or capecitabine label or local clinical guidances, for DPD status recommendation prior to starting treatment.
6. Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype:
a. SLI: Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype will be excluded from Cohort 1 (EC + FOLFIRI) of the SLI.
b.Phase III: Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype may be enrolled, but may not receive FOLFOXIRI if randomized to the Control Arm.
c. Cohort 3: Participants with documented Gilbert's syndrome or known homozygous UGT1A1*28/*28 or UGT1A1*6/*6 genotypes or double heterozygous UGT1A1*6/*28 genotype will be excluded from Cohort 3 Arm D and Arm E (EC + FOLFIRI and FOLFIRI ± bevacizumab).
7. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
8.Colorectal adenocarcinoma that is RAS mutant or for which RAS mutation status is unknown.
9. Locally confirmed dMMR or MSI-H colorectal carcinoma or unknown MSI/MMR status. If participant is is locally confirmed dMMR or MSI-H and unable to receive immune checkpoint inhibitors due to a pre-existing medical condition, they may be enrolled.

Screening Exclusion Criteria
10. Impaired gastrointestinal function (eg, uncontrolled nausea, vomiting or diarrhea, malabsorption syndrome, small bowel resection) or disease which may significantly alter the absorption of oral study intervention or recent changes in bowel function suggesting current or impending bowel obstruction.

11. Clinically significant cardiovascular diseases, including any of the following:
a. History of acute myocardial infarction, acute coronary syndromes (including unstable angina, coronary artery bypass graft, coronary angioplasty or stenting) <=6 months prior to randomization;
b. Congestive heart failure requiring treatment (New York Heart Association Grade Class II and above);
c. Recent history (within 1 year prior to randomization) or presence of clinically significant cardiac arrhythmias (including uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
d. History of thromboembolic or cerebrovascular events <=12 weeks prior to randomization. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (ie, massive or sub-massive) deep vein thrombosis or pulmonary emboli.
Note: Participants with either deep vein thrombosis or pulmonary emboli that do not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.
Note: Participants with thromboembolic events related to indwelling catheters (including PICC lines) or other procedures may be enrolled.
e. Triplicate average QTcF interval >=480 ms or a history of prolonged QT syndrome.
Note: Participants with bundle-branch block (BBB) or with an implanted cardiac pacemaker, may enroll into the study following consultation with the Sponsor.
f. Congenital LQTS.
12. Evidence of active noninfectious pneumonitis.
13. Evidence of active and uncontrolled bacterial or viral infection, with certain exceptions, as noted below, for chronic infection with HIV, hepatitis B or hepatitis C, within 2 weeks prior to start of study intervention.
14. Participants positive for HIV are ineligible unless they meet all of the following:
a. A stable regimen of highly active anti-retroviral therapy that is not contraindicated (see Section 6.5);
b. No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections;
c. A CD4 count >250 cells/mcL, and an undetectable HIV viral load on standard PCR-based tests.

For a full list please see section 5.2 of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-03-2022
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bevacizumab
Generic name:	Avastin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Capecitabine
Generic name:	Xeloda
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cetuximab
Generic name:	Erbitux
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Encorafenib
Generic name:	Braftovi
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Oxaliplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-10-2020
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-01-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-05-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-12-2021
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-04-2023
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Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509405-77-00
EudraCT	EUCTR2020-001288-99-NL
ClinicalTrials.gov	NCT04607421
CCMO	NL75120.028.20