A PHASE 2, RANDOMIZED, OPEN-LABEL STUDY OF ENCORAFENIB AND CETUXIMAB PLUS PEMBROLIZUMAB VERSUS PEMBROLIZUMAB ALONE IN PARTICIPANTS WITH PREVIOUSLY UNTREATED BRAF V600E-MUTANT, MSI-H/DMMR METASTATIC COLORECTAL CANCER

Published: 04-04-2022
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This study has been transitioned to CTIS with ID 2024-512119-34-00 check the CTIS register for the current data. Comparing the efficacy of encorafenib and cetuximab plus pembrolizumab (triplet group [group A]) vs. pembrolizumab (control group [group...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56187

Source
ToetsingOnline

Brief title
SEAMARK

Condition

- Other condition
- Metastases

Synonym
colorectal cancer and bowel cancer

Health condition

Gemetastaseerd colorectale kanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cetuximab, Colorectal cancer, Encorafenib, Pembrolizumab

Outcome measures

Primary outcome

Progression free survival per investigator, defined as the time from

randomization to disease progression based on RECIST v1.1, or to death from any

cause, whichever occurs first.

Secondary outcome

Incidence and severity of adverse reactions classified according to the NCI

CTCAE v4.03 and changes in clinical laboratory test parameters, vital signs and

ECGs.

Incidence of dose interruptions, dose adjustments, and permanent

discontinuations associated with adverse reactions.

Overall survival, defined as time from randomization to date of death from any cause.

Objective response, defined as confirmed complete response or confirmed partial response based on investigator assessment according to RECIST v1.1, from the date of randomization to the date of first documentation of progressive disease (PD), death, or initiation of new anticancer therapy.

Duration of response, defined as the time from first response to PD based on investigator assessment according to RECIST v1.1 or death from any cause, whichever occurs first.

BRAF and MSI status as determined by retrospective central testing of tumor tissue at baseline.

EORTC QLQ-C30: Change from baseline in general health status/QoL, functional and symptom scales, and individual items.

• EQ-5D-5L: change from baseline in index score and VAS,

• PGIS Score: Change from Baseline in Score

• PGIC score

Study description

Background summary

Approximately 20-25% of metastatic colorectal cancer (mCRC) tumors with BRAF V600E mutation are also MSI-H/dMMR (Venderbosch et al, 2014; André et al, 2020). The combined presence of a BRAF mutation and MSI-H/dMMR is associated with a poorer prognosis which is believed to be primarily driven by the BRAF mutation (Venderbosch et al, 2014). The encorafenib + cetuximab regimen was approved in the US and EU in patients with previously treated mCRC with BRAF V600E mutation based on data from the Phase 3 study BEACON in which patients treated with encorafenib + cetuximab showed statistically significant improvements compared to standard chemotherapy (Kopetz et al, 2019). The PD-1 inhibitor pembrolizumab has been approved for the treatment of patients with treatment-naïve mCRC who were MSI-H/dMMR based on the results of the Phase 3 study KEYNOTE-177 (NCT02563002) in which patients were randomized to receive pembrolizumab as monotherapy or standard first-line mCRC chemotherapy.

The rationale for combining encorafenib and cetuximab with pembrolizumab lies in the hypothesis that tumor progression in these patients is driven by both genomic instability, reflected by an MSI-H/dMMR status, mediating susceptibility to checkpoint inhibition, as well as MAPK signaling, which is driven by mutation in BRAF, which in turn functions as a dominant driver for oncogene and EGFR signaling. Combining pembrolizumab with encorafenib and cetuximab is thus believed to demonstrate greater antitumor activity in patients with mCRC that is both MSI-H/dMMR and BRAF mutated than pembrolizumab or encorafenib+cetuximab alone.

Study objective

This study has been transitioned to CTIS with ID 2024-512119-34-00 check the CTIS register for the current data.

Comparing the efficacy of encorafenib and cetuximab plus pembrolizumab (triplet group [group A]) vs. pembrolizumab (control group [group B]).
Assessing the overall safety and tolerability of group A vs. group B.
Assessing the efficacy of group A vs. group B.
Confirming BRAF and MSI status in tumor tissue.
Assessing the effect on PROs of group A vs. group B.
Understanding the relationship between the studied therapeutic intervention(s) and the biology of the participant's disease.
Understanding the surgical conversion rate of group A vs. group B.

Study design

This is an open-label, randomized Phase 2 study investigating encorafenib and cetuximab plus pembrolizumab (triplet group [group A]) versus pembrolizumab alone (control group [group B]) as first-line treatment in participants with metastatic colorectal cancer (mCRC) testing positive for MSI-H/dMMR and BRAF V600E mutation.

Approximately 104 participants in approximately 90 study centers in approximately 16 countries will be randomized 1:1 to encorafenib and cetuximab plus pembrolizumab (group A) or pembrolizumab (group B) (approximately 52 participants per group).
Participants will receive up to 18 administrations (approximately 2 years) of pembrolizumab; however, Arm A treatment group can continue to receive encorafenib and cetuximab after this period if indicated by treating physician.
Each cycle of treatment will last 42 days.

Intervention

Participants will receive either encorafenib (300 mg orally once daily) + cetuximab (500 mg/m2 Q2W IV) once every 2 weeks + pembrolizumab (400 mg Q6W IV) once every 6 weeks or just pembrolizumab (400 mg Q6W IV). Study treatment will be administered until disease progression according to RECIST v1.1 data or until one of the other protocol-defined criteria for study treatment discontinuation is met. In certain circumstances, continuation of treatment after disease progression may be allowed. In both treatment groups, the duration of treatment with pembrolizumab will not exceed 18 administrations (approximately 24 months).

Study burden and risks

Physical exam including measurement of height, weight, blood pressure, respiratory rate, heart rate, temperature, eye exam and a skin exam.
Performance status assessment.
Blood samples for routine testing, tumor markers, thyroid function, testing for hepatitis and HIV (if needed), and biomarker tests. cycle 1 blood volume = approximately 55ml and future cycles = approximately 25ml (excluding biomarker samples).
Pregnancy test for women.
ECG measurements.
CT, PET-CT or MRI scan of the chest, abdomen, and pelvis and, if necessary, and MRI scan of the brain.
Possibility for new tumor sample if no archive biopsy available or insufficient during pre-screening.
Questionnaires regarding quality of life on an electronic tablet (EORTC QLQ-C30, EQ-5D-5L, PGIS, PGIC).
Completion of encorafenib dose diary (group A only).

Drug risk (Most common)
Encorafenib:

•Constipation
• Decreased appetite
• Diarrhea

• Sleep problems
• Dry skin
• Tired feeling
• Fever
• Hair loss
• Headache
• Itch
• Muscle or joint pain
• Nausea
• Pain, such as pain in arms, legs and back
• Redness, swelling, numbness and peeling of the skin on the palms of the hands and soles of the feet (hand-foot skin reaction)
• Skin rashes including redness, itching, hives and swollen patches of skin
•Skin redness
•Skin tags, new moles on the skin or changes in existing moles
•Small, rough bumps on the skin
• Thickening of external part of the skin
• Tingling, numbness or abnormal sensitivity to pain or touch and nerve pain
• Vomit
• Weakness

Cetuximab:

• Skin reactions, mainly acne-like rashes (inflamed hair follicles, acne and rash) and/or less commonly as itchy, dry skin,
scaling of the skin, excessive hair growth, or nail disorders, manifesting as pain, tenderness, and tearing of fingernails and toenails
• During or shortly after the cetuximab infusion, you may experience mild to moderate infusion-related reactions such as fever and chills, dizziness, respiratory distress
• Inflammation of the gut wall, mouth and nose (in some cases severe), which can lead to nosebleeds in some patients
• Decrease in the concentration of magnesium in the blood
• Increase in blood levels of certain liver enzymes

Pembrolizumab:

• itchy skin
• loose or watery stools
• cough

Contacts

Public

Pfizer

Rivium Westlaan 142
Capelle a/d IJssel 2909LD
NL
Scientific
Pfizer

Rivium Westlaan 142
Capelle a/d IJssel 2909LD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

Histologically or cytologically confirmed metastatic Stage IV colorectal adenocarcinoma
Availability of adequate tumor tissue
Locally confirmed dMMR or MSI-H disease in tumor tissue or blood
Locally confirmed BRAF V600E mutation in tumor tissue or blood
Presence of measurable disease per RECIST v1.1
No prior systemic regimens for metastatic disease

Exclusion criteria

Colorectal adenocarcinoma for which RAS mutant or RAS mutation status is unknown.
Known active CNS metastases and/or carcinomatous meningitis; leptomeningeal disease.
Immunodeficiency or active autoimmune disease requiring systemic treatment in

the past 2 yrs.
Presence of acute or chronic pancreatitis.
History of chronic inflammatory bowel disease requiring medical intervention <= 12 months prior to randomization.
Impaired GI function or disease which may significantly alter the absorption of oral study drug
Clinically significant cardiovascular diseases (eg, thromboembolic or CVA events <= 12 wks prior).
Current noninfectious pneumonitis or history of noninfectious pneumonitis requiring steroids.
Evidence of active and uncontrolled bacterial or viral infection.
Previous treatment with BRAF inhibitor or any EGFR inhibitor or an immune checkpoint inhibitor
Receipt of immune-enhancing or suppressive treatments <= 14 days prior to randomization.
Participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease are not eligible.
Receipt of a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-08-2022
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Bravtovi
Generic name:	Encorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-04-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-06-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-08-2022

Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-02-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-03-2024

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	CTIS2024-512119-34-00
EudraCT	EUCTR2021-003715-26-NL
ClinicalTrials.gov	NCT05217446
CCMO	NL80567.028.22