An Open-label Randomized Phase 3 Study of Tucatinib in Combination with Trastuzumab and mFOLFOX6 versus mFOLFOX6 given with or without either Cetuximab or Bevacizumabas First-line Treatment for Subjects with HER2+Metastatic Colorectal Cancer

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To evaluate the efficacy and safety of tucatinib in combination with trastuzumab and mFOLFOX6 in comparison to mFOLFOX6 given with or without either bevacizumab or cetuximab as first-line (1L) treatment in adults with HER2 positive (HER2+)…

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

Summary

ID

NL-OMON56153

Source
ToetsingOnline

Brief title
MOUNTAINEER-03 / CIV-ID PS-22-07-040046

Condition

- Other condition

Synonym
HER2+ mCRC, HER2+ metastatic colorectal cancer

Health condition

Gastrointestinal disorders, Colorectal Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Seagen Inc., a wholly owned subsidiary of Pfizer
Source(s) of monetary or material Support: The Pharmaceutical Study Sponsor will be contracting with the collection sites

Intervention

Keyword: HER2+ Metastatic Colorectal Cancer, mFOLFOX6, Trastuzumab, Tucatinab

Outcome measures

Primary outcome

Primary Objective:

To compare progression-free survival (PFS) per Response Evaluation Criteria in

Solid Tumors 1.1 (RECIST v1.1) according to blinded independent central review

(BICR) assessment between treatment arms.

Secondary outcome

Secondary Objectives:

• To compare overall survival (OS) between treatment arms

• To compare confirmed objective response rate (cORR) per RECIST v1.1 according

to BICR assessment between treatment arms

• To assess PFS per RECIST v1.1 according to investigator (INV) assessment

• To evaluate cORR per RECIST v1.1 according to INV assessment

• To evaluate duration of response (DOR) per RECIST v1.1 according to BICR

assessment

• To evaluate DOR according to INV assessment

• To evaluate time from randomization to disease progression on next-line treatment or death from any cause (PFS2)

• To assess the overall safety profiles by the treatment arms

• To evaluate the pharmacokinetics (PK) of tucatinib

• To assess the change from baseline in selected items of the global health status/quality of life (QoL), physical functioning, and appetite loss by treatment arms using the European Organization for Research and Treatment of Cancer Quality of Life 30-item core questionnaire (EORTC QLQ-C30)

• To assess the time to meaningful change in global health status/QoL, physical functioning and appetite loss by treatment arms using the EORTC QLQ-C30

Study description

Background summary

Please refer to Protocol Section 5. INTRODUCTION

Study objective

To evaluate the efficacy and safety of tucatinib in combination with trastuzumab and mFOLFOX6 in comparison to mFOLFOX6 given with or without either bevacizumab or cetuximab as first-line (1L) treatment in adults with HER2 positive (HER2+) metastatic colorectal cancer (mCRC).

Study design

Study Design:
This is a global, open label, randomized, phase 3, multicenter study to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and mFOLFOX6 in comparison to mFOLFOX6 given with or without either bevacizumab or cetuximab as 1L treatment in adults with HER2+ mCRC. Eligible participants must have locally advanced unresectable or metastatic colorectal cancer (mCRC) that is HER2+, RAS WT, and must not have received systemic treatment for CRC in

the metastatic setting except for a maximum of 2 doses of mFOLFOX6 in the locally advanced unresectable or metastatic setting prior to randomization. HER2 status will be determined via central lab testing during the screening period using investigational HER2 immunohistochemistry (IHC) and in situ hybridization (ISH) assays to support companion diagnostic development. The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) gastric and gastroesophageal cancer guidelines will be used to identify participants who are HER2+ with an immunohistochemistry (IHC) 3+ or IHC 2+/in situ hybridization positive (ISH+) result. Participants are required to have RAS WT status as determined by local or central testing; central testing may only be used with Medical Monitor approval if local testing is not available or when otherwise deemed necessary (for central RAS testing, tissue must be submitted prior to study enrollment and must be analyzed within 1 year of biopsy date).

The study consists of 2 arms. Approximately 400 participants will be randomized in a 1:1 fashion to either the tucatinib experimental arm or the standard of care (SOC) control arm. Randomization will be stratified by the following factors: primary tumor location (left sided versus all other [right, transverse, overlapping]), presence or absence of liver metastases, and number of doses of mFOLFOX6 chemotherapy prior to randomization (0, 1, or 2). Participants in the tucatinib experimental arm will receive tucatinib in combination with trastuzumab and mFOLFOX6. Participants in the SOC control arm will receive mFOLFOX6 given with or without either bevacizumab or cetuximab per investigator*s decision. The regimen to be used in the SOC control arm should be chosen before randomization, and all SOC regimens must start at doses stipulated in the protocol. Participants must remain on their originally assigned treatment regimen; however, individual components within a regimen may be discontinued at the discretion of the investigator if it is in the participant*s best interest. Crossover from the SOC control arm to the tucatinib experimental arm is not permitted. Participants may be rescreened once after initially failing to meet the inclusion/exclusion criteria.

Higher than expected incidence rate of adverse events of diarrhea have been observed in participants with advanced gastrointestinal (GI) cancers who received the combination of tucatinib, trastuzumab, and FOLFOX in an ongoing phase 1b/2 study. In the current phase 3 study, antidiarrheal prophylaxis with loperamide will be required for all participants on the tucatinib experimental arm for Cycle 1 of study treatment only. The dosing of loperamide will be adjusted by the investigator for all subsequent cycles, as appropriate.

Intervention

The study consists of 2 arms. Approximately 400 subjects will be randomized in a 1:1 fashion to either the tucatinib experimental arm or the standard of care (SOC) control arm.

Tucatinib experimental arm:
Tucatinib will be administered at a dose of 300 mg orally (PO) twice daily (BID). Trastuzumab will be administered every 3 weeks (Q3W), with a loading dose of 8 mg/kg intravenously (IV) on Cycle 1 Day 1 only, followed by 6 mg/kg IV on Cycle 1 Day 22 then Day 1 and Day 22 of each subsequent 6-week (42-day) cycle thereafter, except in specific circumstances where trastuzumab may be give weekly to compensate for modifications in treatment schedule. mFOLFOX6 will be administered every 2 weeks on Days 1, 15, and 29 of each 6-week (42-day) cycle and consists of oxaliplatin 85 mg/m2 IV, leucovorin 400 mg/m2 IV (or levoleucovorin 200 mg/m2 IV; leucovorin or levoleucovorin is administered concurrently with oxaliplatin via separate IV lines), 5-fluorouracil 400 mg/m2 (IV bolus), then 5-fluorouracil 2400 mg/m2 (IV administration over 46-48 hours).

Beginning on Cycle 1 Day 1, for all participants in the tucatinib experimental arm, loperamide will be administered at a dose of 4 mg three times daily for the first 14 days (Days 1-14), followed by 4 mg twice daily on Days 15-42.

Standard of care (SOC) control arm:
Participants randomized to the SOC control arm will receive mFOLFOX6 given with or without either bevacizumab or cetuximab at the investigator*s discretion. The investigator*s choice of control arm regimen must be made prior to randomization. Participants must remain on their originally assigned treatment regimen; however, individual components within a regimen may be discontinued at the discretion of the investigator if it is in the participant*s best interest. mFOLFOX6 will be administered every 2 weeks on Days 1, 15, and 29 of each 6 week (42 day) cycle and consists of oxaliplatin 85 mg/m2 IV, leucovorin 400 mg/m2 IV (or levoleucovorin 200 mg/m2 IV; leucovorin or levoleucovorin is administered concurrently with oxaliplatin via separate IV lines), 5 fluorouracil 400 mg/m2 (IV bolus), then 5 fluorouracil 2400 mg/m2 (IV administration over 46-48 hours).

Bevacizumab 5 mg/kg will be administered IV every 2 weeks (Days 1, 15, and 29 of each 6 week [42 day] cycle) during each 6 week (42 day) cycle.

Cetuximab will be administered 400 mg/m2 IV over 2 hours on Cycle 1 Day 1, followed by 250 mg/m2 IV over 1 hour for each subsequent weekly dose during each 6 week (42 day) cycle.

All subjects will be receive a radiographic assessment for progressive disease per blinded independent central review (BICR). They will be subjected to a safety and survival follow-up (follow-up will include assessment of PFS2). Subjects may continue on treatment until disease progression per RECIST v1.1 by BICR, unacceptable toxicity, withdrawal of consent, or study termination,

whichever occurs first

Study burden and risks

TUCATINIB COMMONLY REPORTED RISKS AND SIDE EFFECTS:
Most of the people who took tucatinib were cancer patients. Some people who took tucatinib were healthy volunteers who did not have cancer.
Patients with cancer who were treated with only tucatinib included 50 patients in total. These patients had the side effects listed below.
These side effects may or may not be directly related to tucatinib. They could be related to cancer or other medical problems.
- Feeling sick to stomach (nausea)
- Watery poop (diarrhea)
- Feeling tired (fatigue)
- Throwing up (vomiting)
- Rash
- Difficulty pooping (constipation)
- Cough
- Pain in arms or legs (pain in extremity)
- Back pain
- Headache
- Infection that could cause frequent and painful urination (urinary tract infection)
- Muscle pain (myalgia)
- Muscle and bone pain in chest (musculoskeletal chest pain)
- Belly pain (abdominal pain)
- High levels of liver enzymes (increased liver function tests). This may mean the patient has a problem with his/her liver.
- Not wanting to eat (anorexia)
- Feeling dizzy (dizziness)
- Feeling out of breath (dyspnea)
- Patchy redness on skin (erythema)
- Low levels of magnesium in your blood (hypomagnesemia). Participants may feel weak, have an abnormal heartbeat, muscle cramps, or seizures.
- Heavy sweating while sleeping (night sweats)
- Infection in the nose, sinuses or throat (upper respiratory tract infection). Participants may have fever, pain, or a hard time breathing.

Also liver function problems, severe diarrhea and increased creatinine levels have been reported.
The other drugs used in this study (trastuzumab, mFOLFOX6 (which consists of oxaliplatin, leucovorin or levoleucovorin, and fluorouracil), cetuximab and bevacizumab) can also have side effects. As these are marketed drugs, please refer to the Patient Information Leaflet.

RISKS AND SIDE EFFECTS OF TUCATINIB, TRASTUZUMAB AND MFOLFOX6 TOGETHER:
There may also be side effects that come from getting tucatinib with

trastuzumab, and mFOLFOX6 that are not found (or are not as serious) in people who only take one of these drugs.

RISKS OF THE EXPERIMENTAL HER2 ASSAYS:
These experimental tests will check to see if participants' cancer cells make HER2. These tests are still being developed for your disease. There is a chance that the test might not work to find participants who are most likely to respond to the study drugs.

RISKS OF THE TUMOR BIOPSY:
The risks of tumor biopsy include possible pain, discomfort, bleeding, swelling, scarring, bruising and infection. To reduce these risks, the site of the biopsy will be numbed, and sterile techniques will be used.
Furthermore participants may have discomforts from the intravenous infusion or blood draws (irritation or bruises); from the CT scans or MRIs (claustrophobic sensation, reactions to the contrast agent, minimal radiation risk), from the MUGA scan (reaction to tracer, minimal radiation risk) or from the ECG (skin irritation, slight redness or burning of the skin at the site where the leads were attached).

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria
Participants must meet the following key inclusion criteria to be eligible for the study:
• Have histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is locally advanced unresectable or metastatic
• Participants must be willing and able to provide the most recently available formalin fixed paraffin embedded tumor tissue blocks (or freshly sectioned slides, see laboratory manual for details), obtained prior to treatment initiation, to a sponsor designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly obtained baseline biopsy of an accessible tumor lesion is required within 35 days prior to the Cycle 1 Day 1 timeframe. Biopsy must provide adequate tissue for analysis; the following biopsy types are acceptable: resection, excision, punch (skin lesions only) and core needle biopsies.
• Have HER2+ disease as determined by tissue based investigational HER2 IHC and ISH assays performed at a sponsor defined central laboratory. HER2 amplification will be determined using ASCO/CAP guidelines for gastric and gastroesophageal cancer with IHC 3+ or IHC 2+/ISH+ result.
• Have RAS WT disease as determined by local or central testing. Central testing may only be used with Medical Monitor approval if local testing is not available or when otherwise deemed necessary. For central RAS testing, tissue must be submitted prior to study enrollment and analyzed within 1 year of biopsy date.
• Have radiographically measurable disease per RECIST v1.1 according to INV assessment, with at least one site of disease that is measurable and that has not been previously irradiated; or, if the participant has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation
• Have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
• CNS Inclusion*Based on screening contrast brain magnetic resonance imaging (or CT with contrast if MRI is contraindicated), participants may have any of the following:
a. No evidence of brain metastases
b. Previously treated brain metastases which are asymptomatic
* Brain metastases previously treated with local therapy must not have progressed since treatment
* Time since whole brain radiation therapy (WBRT) is >= 14 days prior to

enrollment, time since stereotactic radiosurgery (SRS) is >= 7 days prior to enrollment, or time since surgical resection is >= 28 days prior to enrollment
* Relevant records of any CNS treatment must be available to allow for classification of target and non target lesions

Exclusion criteria

Exclusion Criteria
Participants will be excluded from the study for any of the following key exclusion criteria reasons:
• Have previously received any systemic anticancer therapy for CRC in the locally advanced unresectable or metastatic setting or have participated in any interventional clinical trial for CRC in the locally advanced unresectable or metastatic setting; note that participants may have received a maximum of 2 doses of mFOLFOX6 in the locally advanced unresectable or metastatic setting prior to randomization.
Note: participants may have received prior chemotherapy for CRC in the adjuvant setting provided that it was completed >6 months prior to enrollment.
• Have previously received radiation therapy within 14 days prior to enrollment (or within 7 days in the setting of SRS). Participants who have received prior radiation therapy must have recovered to baseline from any treatment related adverse events (AEs). Participants who have received palliative radiotherapy for symptomatic metastases may enter the study without a washout period provided that the participant has recovered from any treatment related AEs.
• Have previously been treated with anti HER2 therapy
• Have ongoing >= Grade 2 diarrhea of any etiology
• Inability to swallow pills or any significant GI disease which would preclude the adequate oral absorption of medications
• Participants with active CNS metastases (irradiated or resected lesions are permitted, See Inclusion Criteria for details). Participants with carcinomatous meningitis are excluded without exception.

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-01-2024
Enrollment:	16
Type:	Actual

Medical products/devices used

Generic name:	VENTANA HER2/neu (4B5) IUO assay and VENTANA HER2 Dual ISH DNA probe Cocktail
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tukysa
Generic name:	Tucatinib (PF-07265792)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-06-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-04-2025
Application type:	Amendment
Review commission:	METC NedMec

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
EudraCT	EUCTR2021-002672-40-NL
ClinicalTrials.gov	NCT05253651
CCMO	NL81869.000.23