A Dose-Escalating Phase I/II Study in Patients with RAS-Mutated Metastatic Colorectal Cancer to Investigate Safety and Clinical Activity of the Triple Combination of: MEK-inhibitor binimetinib, Pan-EGFR inhibitor lapatinib and the Microtubule Targeting Agent (MTA) vinorelbine.

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Primary Objective: Phase I dose escalationThe main objective of the phase I part is to determine safety and the recommended phase II dose (RP2D) of the triple combination.Phase IIThe main objective of the phase II part is to determine efficacy of...

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

Summary

ID

NL-OMON54073

Source
ToetsingOnline

Brief title
RASTRIC Trial

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
RAS-mutated metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Oncode

Intervention

Keyword: metastatic colorectal cancer, RAS mutated, triple combination

Outcome measures

Primary outcome

For the phase I dose-escalation trial:

The primary endpoint is the incidence of DLTs leading to a RP2D. The RP2D of the triplet will be the MTD which is defined as the dose level that can be given to 6 subjects such that not more than 1 subject experiences a DLT.

For the phase II trial:

The primary endpoint is best overall response (OR), defined as complete response (CR) + partial response (PR) within 6 months, based on RECIST 1.1.

Secondary outcome

• Safety and tolerability assessed by:

o Incidence and severity of adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

o Incidence of dose interruptions, dose modifications and

discontinuations due to AEs

• The pharmacokinetic (PK) profile of vinorelbine, lapatinib and binimetinib.

• Clinical benefit, defined as CR + PR + stable disease (SD) for at least 6

months.

• Progression-free survival (PFS), defined as the time from the date of

randomization until the date of the investigator-assessed radiological

disease progression (RECIST 1.1) or death due to any cause.

Study description

Background summary

Patients with RAS-mutated metastatic colorectal cancer (mCRC) have a poorer overall survival and less therapeutic options compared to patients with RAS-wildtype mCRC. RAS-mutated (RASm) tumors are found to be resistant to anti-EGFR therapy. A combination of MEK-inhibition and pan-EGFR inhibition was evaluated in a phase I trial for patients with RASm mCRC to overcome this resistance. This combination has proven to be safe, however limited responses were seen, although active drug levels were reached in tumor tissue. Drug screens performed on a range of patient-derived RASm organoids showed that the MEK-pan-EGFR combination is cytostatic rather than cytotoxic, and addition of a low dose of a Microtubule Targeting Agent (MTA) like vinorelbine resulted in remarkable synthetic lethality. We propose that addition of an MTA to the combination of the MEK-inhibitor binimetinib and the pan-EGFR-inhibitor lapatinib will result in anti-tumor efficacy in patients with RASm mCRC.

Study objective

Primary Objective:
Phase I dose escalation
The main objective of the phase I part is to determine safety and the recommended phase II dose (RP2D) of the triple combination.

Phase II
The main objective of the phase II part is to determine efficacy of the triplet combination defined by objective response rate according to RECIST 1.1.

Secondary Objectives:

Phase I dose escalation
- To describe safety and tolerability of the triplet combination
- To describe the pharmacokinetic profile of vinorelbine, lapatinib and binimetinib.

Phase II
- To describe safety and tolerability of the triplet combination
- To evaluate additional antitumor activity parameters including clinical benefit rate and progression-free survival.
- To describe the pharmacokinetic profile of vinorelbine, lapatinib and binimetinib. To compare the serum concentration measurements with drug concentration measurements in the biopsy after two weeks of treatment.

Exploratory objectives:
Exploratory pharmacodynamics (inhibition of downstream targets and apoptosis) and the use of organoids as predictive biomarker will be assessed. Furthermore a sub study will be performed on the correlation between cardiotoxicity (LVEF decline) and the release of cardiac biomarkers. Finally, blood samples will be stored to allow the analyses of additional biomarkers including circulating tumor DNA (ctDNA).

Study design

This is a single-centre dose-escalating phase I/II trial evaluating the triplet combination of the MEK-inhibitor binimetinib, the pan-EGFR-inhibitor lapatinib with vinorelbine in RAS-mutated metastatic colorectal cancer. The trial consists of a phase I dose-finding study (3 + 3 classical design) evaluating the RP2D of the triplet and a phase II study evaluating response rate and safety following a Simon*s two stage design. The patients from the phase I trial treated at the MTD will be included in the phase II analysis. In total between 47-50 patients will be included depending on the dose escalation.

Intervention

In the initial dose levels, a rest week schedule was tested to reach an appropriate level for the three drugs with manageable side-effects. In later dose levels, an every-week schedule is tested to optimize efficacy of the therapy.

Rest week schedule:
Treatment cycles consist of 21 days. Lapatinib and binimetinib are administered orally, respectively once and twice a day, in a 5 days on/2 days off schedule in the first and second week of every cycle. Vinorelbine is given in a day 3 and day 10 schedule intravenously. The third week is a rest week.

Every-week schedule:
Treatment cycles consist of 21 days. Lapatinib and binimetinib are administered orally, respectively once and twice a day, in a 5 days on/2 days off schedule every week of every cycle. Vinorelbine is given in a day 3, day 10 and day 17 schedule intravenously.

Adapted every-week schedule:
Treatment cycles consist of 21 days. Lapatinib and binimetinib are administered orally, respectively once and twice a day, in a 5 days on/2 days off schedule every week of every cycle. Vinorelbine is given in a day 3 and day 10 schedule intravenously.

Study burden and risks

The combination of drugs can cause adverse effects. During visits to the hospital, the patient will be regularly examined. In addition, patients will have to follow strict instructions on how to monitor their health and when to call to the hospital.
The burden within this study is that these visits ask for a large time investments and will require more tests and examinations than they would be subjected to if they would follow a regular new treatment line.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histological or cytological proof of CRC.
2. After failure of a minimum of 2 lines of standard of care regimens. Prior lines of treatment must include: a minimum of 2 lines of prior systemic treatment for metastatic disease, including at least fluoropyrimidine, oxaliplatin and irinotecan based treatment (unless contra-indications for either oxaliplatin and/or irinotecan). Adjuvant treatment completed < 6 months before development of metastatic disease will be counted as 1st line for metastatic disease.
3. Written documentation of a known pathogenic RAS mutation.
4. Age * 18 years.
5. Able and willing to give written informed consent.
6. Measurable disease according to RECIST 1.1
7. WHO performance status of 0 or 1.
8. Able to swallow and retain orally administered medications and does not have clinically significant gastrointestinal abnormalities that may alter absorption (e.g. malabsorption syndrome, ileostomy or major resection of the stomach or bowel)
9. Able and willing to undergo blood sampling.
10. Able and willing to undergo a tumor biopsy prior to start and after two weeks on therapy. Tumor biopsy should be histological. Cytological biopsies are not accepted.
11. All toxicities related to prior treatment should have resolved to CTCAE grade 1 or less (excluding alopecia)
12. Life expectancy * 3 months allowing adequate follow up of toxicity evaluation and antitumor activity.
13. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration and agree to use effective contraception, throughout the treatment period, and for 4 months after the last dose of study treatment.
14. Adequate organ functions:
Absolute neutrophil count >= 1.5 x 109/L
Hemoglobin >= 6.0 mmol/L
Platelets >= 100 x 109/L
PT/INR and aPTT within normal limits (unless anti-coagulant treatment)
Total bilirubin <= 1.5 x ULN
AST and ALT <= 2.5 x ULN or <= 5x ULN in case of liver metastases
Albumin >= 30.0 g/L

Lactate dehydrogenase <= 2x ULN
Serum creatinine <= 1.5 x ULN or Calculated creatinine clearance by Cockcroft-Gault formula: >= 50 mL/min
Left Ventricular Ejection Fraction (LVEF) by ECHO or MUGA >= 50%

Exclusion criteria

1. Any treatment with investigational drugs within 30 days or 5 half-lives prior to receiving the first dose of investigational treatment.
2. History of another malignancy. Exceptions: Patients who have been disease-free for at least 3 years after treatment with curative intent, or patients with a history of completely resected non-melanoma skin cancer, in situ carcinoma of the cervix and/or patients with indolent completely resected second malignancies are eligible.
3. Symptomatic or untreated leptomeningeal disease.
4. Symptomatic brain metastases. Patients previously treated or untreated for these conditions that are asymptomatic in the absence of corticosteroid and anticonvulsant therapy (for at least 6 weeks) are allowed to enrol. Radiotherapy for brain metastases must have been completed at least 6 weeks prior to start of study treatment. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening demonstrating no current evidence of progressive brain metastases). Patients are not permitted to receive anti-epileptic drugs or corticosteroids.
5. Patients previously treated with combination treatment of drugs known to interfere with EGFR, HER-2, HER-3, HER-4, or MAPK- and PI3K-pathway components, including inhibitors of PTEN, PI3K, AKT, mTOR, BRAF, MEK, and ERK. Single agent targeted therapies interfering with these pathways are allowed for inclusion in phase I.
Exclusion criteria in phase II: patients previously treated with drugs known to interfere with EGFR, HER-2, HER-3, HER-4, or MAPK- and PI3K-pathway components, including inhibitors of PTEN, PI3K, AKT, mTOR, BRAF, MEK, and ERK, both as single agent or in combination.
6. History of interstitial lung disease or pneumonitis
7. Women who are pregnant or breast feeding.
8. Unreliable contraceptive methods. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms).
9. Radio-, immuno- or chemotherapy within the last 4 weeks prior to receiving the first dose of investigational treatment. Palliative radiation (1x 8Gy) is allowed.
10. Patients who have undergone any major surgery within the last 3 weeks prior to starting study drug or who would not have fully recovered from previous surgery.
11. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1

or HIV-2 type patients.
12. Patients with known, active, hepatitis B (HBV) or C virus (HCV).
13. Patients with retinal degenerative disease (hereditary retinal degeneration or age-related macular degeneration), or with a history of uveitis, retinal vein occlusion, central serous retinopathy, or retinal detachment.
14. Patients with left ventricular ejection fraction (LVEF) < 50%.
15. History or evidence of cardiovascular risk including any of the following:
• A QT interval corrected for heart rate using the Bazett*s formula (QTcB; Appendix X) *480 msec.
• History or evidence of current clinically significant uncontrolled arrhythmias. Exception: Subjects with controlled atrial fibrillation for >30 days prior to randomization are eligible.
• History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
• History of or current congestive heart failure >= class II as defined by the New York Heart Association.
• Treatment refractory hypertension defined as a blood pressure of systolic > 150 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by one maximally dosed anti-hypertensive therapy.
• Patients with intra-cardiac defibrillators.
16. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
17. Known hypersensitivity to one of the study drugs.
18. Use of any live vaccines against infectious diseases (e.g. varicella, pneumococcus or yellow fever) within 4 weeks of initiation of study treatment.
19. Use of prohibited co-medication or herbs and inability to discontinue this treatment or switch to an alternative drug at least 7 days prior to starting study treatment. (see paragraph 5.8.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-08-2020
Enrollment:	50
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Mektovi
Generic name:	Binimetinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Navelbine
Generic name:	Vinorelbine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tyverb
Generic name:	Lapatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-11-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-07-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2024
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	EUCTR2019-004987-23-NL
CCMO	NL72638.041.20