A randomized phase II study of pulsatile high-dose sunitinib versus TAS-102 in patients with metastatic colorectal carcinoma (mCRC).

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON53126

Source
ToetsingOnline

Brief title
SUNRISE-CRC

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic colorectal carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Metastatic colorectal carcinoma, Sunitinib, Targeted Therapy, TAS-102

Outcome measures

Primary outcome

The primary objective is progression-free survival (PFS); defined as the time from randomization to the date of the first documented tumor progression; determined using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria or death due to any cause. We hypothesize that sunitinib will result in a clinically relevant increase in PFS (from 2 months with TAS-102 arm to 5 months with).

Secondary outcome

Secondary objectives include;

- Overall Survival (OS), defined as the time from randomization to the date of death.

- Comparison of QoL parameters between the two study arms. We will use the validated European Organization for Research and treatment of Cancer Quality of Life questionnaires (EORTC QoL), to assess patient reported outcomes during treatment.

- Safety, as reported through the detailed incidence of deaths, adverse events (AE), serious AE, AE leading to discontinuation or dose delay and specific laboratory abnormalities in each treatment arm. Toxicities will be graded using

the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, in combination with patient reported AE*s using the recently developed pro-CTCAE questionnaires.

- Identification of biomarkers that will enable prognosis prediction for the individual patient, pre-treatment classification and response prediction and therapy response monitoring, based on blood diagnostics. This sub aim employs three of the most promising liquid biopsy technologies based on our efforts to develop microRNA, plasma DNA and platelet RNA biomarkers for which preliminary proof of concept has been achieved.

- Health cost analyses.

- Evaluation of protein phosphorylation profiling with phosphoproteomics techniques, as a potential clinical diagnostic tool, to predict for tumor response to targeted therapy in tumor biopsies from metastasis.

Study description

Background summary

Despite the advance in treatment of mCRC, overall survival remains limited and novel, effective approaches are actively pursued. Based on earlier experience that demonstrated encouraging activity and manageable toxicity, this trial proposes the repositioning of an already approved drug, for several tumor types, from a daily lower dose to a higher dose, intermittent scheduling, in patients with mCRC. Angiogenesis plays a crucial role in colorectal cancer growth, proliferation, and metastasizing and it has been investigated as a target for mCRC treatment. Novel drugs blocking the angiogenic pathway, as TAS102, have shown minor significant benefit and has been recently approved for mCRC treatment. Sunitinib has been
previously assessed in patients with mCRC, where it did not demonstrate a meaningful response rate. However, its antiangiogenic mechanism of action makes it plausible, that optimization of the drug itself, namely the scheduling, might result in improved efficacy. Recent trials suggest that intermittent

dosing does not compromise the efficacy of sunitinib, while escalation of the dose at the time of disease progression has been deemed safe and effective. These, taken along with our earlier observations, underscore the scientific validity of our approach. Our alternative treatment strategy with high-dose sunitinib should be interpreted as a chemotherapy-like strategy with a multikinase-inhibitor, shutting off the tumor cell machinery and thereby inducing tumor cell death. If positive, this trial will result in direct clinical implementation, since the aim in benefit is set at 3 months, while a QoL analysis has been integrated in the study protocol according to standard Dutch guidelines (PASKWIL-criteria). The design of this study addresses not only the question whether this new treatment is active but will also determine the position in the line of treatments, as it will establish a new drug of choice. This addition in the lines of treatments could ultimately translate in improved overall survival for the patients, while it offers more space for customized planning of the therapeutic strategy for each individual patient. Simultaneously this trial addresses one of the current challenges in the treatment of mCRC, the population selection via identification of biomarkers, by including an extensive reverse translational approach as a secondary aim. The dedicated tumor and blood sample collection and imaging aims in the identification of new predictive biomarkers and the deciphering of molecular pathways underlining the biology of the disease and the mechanism of action of sunitinib and TAS-102.

Study objective

The primary objective is progression-free survival (PFS); defined as the time from randomization to the date of the first documented tumor progression; determined using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria or death due to any cause. We hypothesize that sunitinib will result in a clinically relevant increase in PFS (from 2 months with TAS-102 arm to 5 months with).

Secondary objectives include;
- Overall Survival (OS), defined as the time from randomization to the date of death.
- Comparison of QoL parameters between the two study arms. We will use the validated European Organization for Research and treatment of Cancer Quality of Life questionnaires (EORTC QoL), to assess patient reported outcomes during treatment.
- Safety, as reported through the detailed incidence of deaths, adverse events (AE), serious AE, AE leading to discontinuation or dose delay and specific laboratory abnormalities in each treatment arm. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, in combination with patient reported AE*s using the recently developed pro-CTCAE questionnaires.
- Identification of biomarkers that will enable prognosis prediction for the individual patient, pre-treatment classification and response prediction and

therapy response monitoring, based on blood diagnostics. This sub aim employs three of the most promising liquid biopsy technologies based on our efforts to develop microRNA, plasma DNA and platelet RNA biomarkers for which preliminary proof of concept has been achieved.
- Health cost analyses.
- Evaluation of protein phosphorylation profiling with phosphoproteomics techniques, as a potential clinical diagnostic tool, to predict for tumor response to targeted therapy in a subgroup of patients willing to undergo an extra tumor biopsy from a metastasis (mandatory for trial participation from 01-2021 onwards).

Study design

Randomized, open label, controlled, intervention phase II/III trial

Intervention

After study inclusion, patients will be randomized (1:1) via a centralized randomization system to receive either oral sunitinib (700 mg once every 2 weeks) or TAS-102 (35 mg per square meter, twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period). Patients will receive treatment until disease progression or discontinuation due to unacceptable toxic effects, withdrawal of consent, or other reason.

During the conduct of the trial an error was observed in the randomization settings (by accident stratification per institute was enabled), causing an imbalance in the treatments groups mainly regarding the stratification factor time. To improve the balance between the groups we made the following changes in consultation with the statistician and the METC:
1. The sample size will be increased with 10 patients (from N = 60 to N = 70)
2. The rest of the patients will be randomized 2:1 in favor of sunitinib
3. Patients will only be stratified for 1 stratification factor:
- time since diagnosis of first metastasis and inclusion (< 18 months versus > 18 months)

Study burden and risks

Adverse effects of TAS-102 monotherapy, considered as a standard treatment in mCRC patients, may occur. Patients randomized for the sunitinib arm may experience physical discomfort or adverse effects. Response to therapy will be measured by CT every 8 weeks (with the possibility to extend with 1 week). Follow-up during therapy will include laboratory analyses together with regularly visits to the outpatient clinic. Additional research blood samples will be taken during regular visits to the outpatient clinic, together with standard safety lab. Patients will be asked to complete quality of life (QoL) forms. Follow-up after therapy, in case of disease progression or

discontinuation due to unacceptable toxic effects, withdrawal of consent, or other reason will be every 12 weeks (to check for Adverse Events and survival).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible for this trial, patients will need to meet all of the following inclusion criteria. Screening must be performed no more than 14 days prior to the first study drug dose., 1: Signed (by the patient or legally acceptable representative) and dated Informed Consent Form (ICF). , 2: Histological or cytological confirmed, documentation of incurable locally advanced or metastatic, colorectal adenocarcinoma, not amenable for potentially curative treatment (i.e. inoperable).
3: Indication for treatment with TAS-102; progressive on (or intolerant to)

therapy including fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy and anti-EGFR therapy (for tumours with wild-type RAS, BRAF and a left sided tumour)). , 4: Evaluable disease by RECIST version 1.1 criteria (see appendix III)., 5: Age >= 18 years. , 6: Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2., 7: Normal 12-lead ECG (clinically insignificant abnormalities permitted)., 8: No signs of clinical thyroid abnormalities (suppletion or blocking drugs permitted)., 9: Adequate bone marrow function; hemoglobin > 5.6 mmol/l, absolute neutrophil count (ANC) > 1,5 x 10*9/l, Platelet count *> 100 x 10*9/l, , 10: Adequate liver function; total bilirubin< 1.5 times the upper limit of normal (ULN), ALT and AST < 2.5 x ULN (In case of liver metastases: <; 5 x ULN)., 11: Albumin higher than 25 g/L, 12: Serum creatinine <;1.5 x ULN or creatinine clearance * 50 ml/min/1.73m2 (based on MDRD)., 13: Pregnant or breast-feeding subjects: Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. For fertile men or women of childbearing potential: documented willingness to use a highly effective means of contraception (e.g., hormonal methods [implants, injectables, or combined oral contraceptives], intrauterine devices, sexual abstinence, or vasectomized or surgically sterilized partner). Contraception is necessary for at least 6 months after receiving the study medication.

Exclusion criteria

The following criteria exclude the patient from enrollment in this trial, 1: Previous treatment with sunitinib and/or TAS-102 for mCRC., 2: Evidence of significant uncontrolled concomitant disease, such as cardiovascular disease (including stroke, New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to screening, unstable arrhythmia, clinically significant valvular heart disease and unstable angina); pulmonary disease (including obstructive pulmonary disease > GOLD 2 and inadequately treated symptomatic bronchospasm), and uncontrolled central nervous system, renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture., 3: Extensive prior radiotherapy in the rectum, pelvis or in more than 3 vertebrae in the spine (less than 3 vertebrae are considered a small radiation field and eligibility will be decided on an individual basis from the PI)., 4: Poorly controlled hypertension despite adequate blood pressure medication. Blood pressure must be <=160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 2 separate measurements., 5: Instable seizure disorders requiring anticonvulsant therapy., 6: Major surgery, other than diagnostic surgery, within 4 weeks prior to day 1, without complete recovery., 7: Uncontrolled bleeding disorders, and/or active bleeding., 8: Known active bacterial, viral, fungal, mycobacterial, or other infection. (including HIV and atypical mycobacterial disease, but excluding fungal infection of the nail beds.), 9: Known hypersensitivity to sunitinib, TAS-102, or to its excipients.,

10: Presence of any significant psychiatric disorder(s) that would interfere with the patient*s compliance., 11: Chemotherapy, radiotherapy, or other anti-cancer therapy within the previous 4 weeks; no nitrosoureas or mitomycin C within the previous 6 weeks; no investigational agents within the previous 4 weeks., 12: Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis., 13: Untreated or active central nervous system (CNS) metastases., 14: Predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline of >3 loose stools daily despite medication., 15: Unresolved bowel obstruction, 16: Any evidence of a disease or condition that might affect compliance with the protocol or interpretation of the study results or render the patient at high risk from treatment complications.

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:	Recruiting
Start date (anticipated):	14-11-2019
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	lonsurf
Generic name:	trifluridine/□tipiracil
Registration:	Yes - NL outside intended use

Product type:	Medicine
Brand name:	sutent
Generic name:	sunitinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-09-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000364-15-NL
CCMO	NL60716.029.18