Organoids to Predict Treatment response In mCRC (OPTIC)

Published: 18-12-2017
Last updated: 16-11-2024

Primary objectives:To validate the concept that ex vivo organoid response correlates to in vivo response to standard treatment in mCRC patients on a metastasis level.Secondary objectives:• Relate organoid results to response to treatment on a…

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54759

Source
ToetsingOnline

Brief title
OPTIC

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colorectal cancer, colorectal carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: UMC Utrecht
Source(s) of monetary or material Support: combinatie UMC Utrecht;HUB en stichting vrienden van het Hubrecht

Intervention

Keyword: metastastic colorectalcancer, organoids, predictive value

Outcome measures

Primary outcome

Primary endpoints:

• Response at first evaluation after treatment with standard of care drugs of the index metastasis that is biopsied for organoid culture as measured by change in size on a CT-scan (continuous variable).

Secondary outcome

Secondary endpoints:

• Response of the index metastasis at second and/or following evaluations (continuous variable)

• Response of the index metastasis dichotomized (< or >20% change in size)

• Response at patient level according to RECIST 1.1

• Progression-free survival

• Repeat above end-points (index metastasis, patient-level response and progression-free survival) for subgroups:

1. per treatment line (e.g. 1st, 2nd or 3rd)

2. per type of treatment given (e.g. irinotecan, oxaliplatin-containing)

• Yield/feasibility of organoid culture

Study description

Background summary

Large randomized clinical trials demonstrate that in the general population systemic treatment offers survival advantage to patients with metastatic cancer. Unfortunately, a significant percentage of patients does not benefit from this treatment but will suffer from the significant side-effects. Being able to identify those patients that will benefit from palliative treatment will be a major advance in personalized treatment of patients with metastatic cancer. At present we are not able to determine tumour drug sensitivity of individual patients on pre- emptive basis. In order to prevent the unnecessary exposure of patients to cytotoxic agents, it is imperative to develop a method that predicts drug sensitivity, optimally guiding therapeutic decision making.

A recent discovery by Sato et al. (2009) and van de Wetering et al., (2015) might offer this opportunity (1,2). They established a culture system (so called: *Organoids*) which allows the unlimited expansion of adult stem cells of various organs which can subsequently be used for functional assays. Importantly, they showed that the Organoids are genetically and phenotypically stable over time (3a, b). The Organoid technology allows the expansion of both healthy and tumor tissue, giving us an array of opportunities to improve health care. One of these opportunities is to use these in vitro expanded tumors (tumor organoids) for ex-vivo drug sensitivity screening.

The OPTIC study in patients with mCRC will assess the value of tumor organoids in therapy response prediction. The study will provide the data to assess the threshold of the screening test to determine a negative predictive value. In addition, the data will provide preliminary data to predict positive treatment response in patients. The study aims to assess the potential value of incorporating organoid technology in the stratification of patients for treatment with anti-neoplastic agents. In addition thereto patients will be offered whole genome sequencing, to be performed by Hartwig. Hartwig is a national non-profit data sequencing centre conducting large scale DNA analysis and combining genomic and clinical data with the aim of stimulating personalised cancer treatment. Furthermore, patients will be asked to contribute the Organoid to the Organoid biobank that is being generated by HUB and UMCU. This Organoid biobank and the data collection associated with it is of great importance to the study of cancer and will benefit from each additional Organoid study and associated data collection.

Study objective

Primary objectives:

To validate the concept that ex vivo organoid response correlates to in vivo

response to standard treatment in mCRC patients on a metastasis level.

Secondary objectives:

• Relate organoid results to response to treatment on a patient level.
• Relate organoid results to progression free survival.
• Examine the predictive value of organoid results within subgroups for response to treatment on a patient level and for progression-free survival.
1. per treatment line (e.g. 1st, 2nd or 3rd)
2. per type of treatment given (e.g. irinotecan, oxaliplatin-containing))
• Assess the discriminative value of the organoid test for patient outcome.
• Explore potential thresholds for the organoid test to yield clinically relevant accuracy for treatment response (sensitivity/specificity/positive and negative predictive value).
• Investigate the feasibility of introducing the organoid test to clinical practice
• To link drug treatment results, both in vitro and in vivo, to genetic characteristics of the tumor. Organoid drug screening and clinical data will be correlated with comprehensive DNA and RNA sequencing results.
• To perform additional organoid screens with potentially non-standard of care drugs based on specific genetic alterations identified by WGS and potentially RNA-sequencing and evaluate the correlation between the genomic information, the drug screen results, and, if available, the patient response.
• To relate blood-derived biomarkers (such as ctDNA, and DNA mutation profiles) to organoid and in vivo metastasis measurements
• Generation of and addition to the Organoid Biobank and distribution from this biobank for future research purposes

Study design

Multicenter observational cohort study. This feasibility study is the first step in the evaluation of tumor organoids as a screening tool to predict treatment response to standard of care drugs in patients with metastatic colorectal cancer. If trial results are promising we will use the data to expand the use of the technology for positive selection/prediction of treatment.

Outcome evaluation for in vivo response to treatment will be performed blinded from in vitro data. The UMCU will collect the clinical data from the participating clinical centers. The HUB will generate the organoid response data from coded patients. At set point HUB will provide this data to the UMCU.

The HUB data will consist of dose response curves that show the response of patient-derived the organoids at specific time points (5 days after seeding) to the SOC standard-of-care (SOC) drugs received by each individual of the specific patient, other SOC options and other experimental compounds.

Hartwig will perform DNA and potentially RNA sequencing on the patient material. Hartwig will generate whole genome sequencing (WGS) data within approximately 10-14 days after blood and biopsy are delivered to Hartwig and provide a patient report and optionally the underlying result files/data to the treating physician to allow use for clinical decision making. Additionally the patient report and underlying result files/data will be shared with UMCU and HUB to correlate with organoid response data and to guide organoid drug screening.

Study burden and risks

For all included patient*s biopsies of the metastatic lesion(s) in the liver, lymph node or subcutaneous lesion will be performed taken in order to obtain material for organoid cultures. Ample experience exists with performing biopsies in patients with metastatic lesions and the procedure is considered to be safe. Alongside the tumor biopsies, up to four blood samples will be obtained, one for screening and up to three to determine germline DNA and for biomarker research. Patients will be treated according to standard of care and clinical management of patients will be performed according to daily practice in participating institutions.

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

1- Patients with histologically proven metastatic colorectal cancer who will receive palliative standard of care systemic treatment, including, but not limited to:
1.1. Capecitabine +/- Bevacizumab (CAP(-B))
1.2. Capecitabine + oxaliplatin +/- Bevacizumab (CAPOX(-B))
1.3. 5FU/LV + oxaliplatin + Bevacizumab (FOLFOX-B)
1.4. 5FU/LV + irinotecan + Bevacizumab (FOLFIRI-B)
1.5. 5FU/LV + oxaliplatin + irinotecan + bevacizumab (FOLFOXIRI-B)
1.6. FOLFIRI + panitumumab (FOLFIRI-P)
1.7. FOLFOX + panitumumab (FOLFOX-P)
1.8. Anti-EGFR monotherapy (cetuximab or panitumumab),
1.9. Irinotecan (IRI)
1.10. Trifluridine + tipiracil hydrochloride (TAS-102)
1.11. Encorafenib + cetuximab
1.12. Treatments outside the above mentioned standard of care regimens (including immune checkpoint inhibitors for dMMR mCRC patients) can be considered, but must be approved by the OPTIC P.I. prior to including patients.

2- Patient is included in PLCRC and has signed informed consent to be asked for future studies and blood withdrawal within PLCRC. , 3- Patients need to have measurable RECIST CT imaging (according to RECIST 1.1) or evaluable disease., 4- Metastatic lesion(s), localized outside the bone, of which a biopsy can safely be obtained as per local guidelines and which is RECIST measurable on CT imaging., 5- Patients not known with contraindications for lidocaine (or its derivatives)., 6- Patients age > 18 years, willing and able to comply with the protocol as judged by the investigator with a signed informed consent.

Exclusion criteria

- Patients with additional unrelated tumors influencing treatment decision making, potentially affecting size changes of metastases or competing risk for survival.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-03-2018
Enrollment:	193
Type:	Actual

Ethics review

Approved WMO Date:	18-12-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	07-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
CCMO	NL61668.041.17