# Pre-operative Administration of Anti-EGFR Monoclonal Antibodies (cetuximab) for the Eradication of Circulating Tumor Cells in Patients Undergoing Curative Treatment of Colorectal Liver Metastases; a dose finding study

Published: 19-09-2016
Last updated: 16-04-2024

The main objective of this study is to determine whether a single neoadjuvant gift of anti-EGFR mAb, administered 48 hours prior to local treatment of colorectal liver metastases, reduces the number of CTCs. Secondary endpoints are determination of...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47303

**Source**
ToetsingOnline

**Brief title**
PremAb-DOSE trial

### Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Hepatic and hepatobiliary disorders

**Synonym**
liver metastases

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W,CCA

## Intervention

**Keyword:** Antibody therapie, colorectal cancer, immunotherapy, liver, metastasis, surgery

## Outcome measures

### Primary outcome

The primary objective of this study is to determine whether a single neoadjuvant gift of the anti-EGFR mAb cetuximab - administered 48 hours prior to local treatment of colorectal liver metastases - reduces the number of circulating tumor cells. Furthermore, we will determine the minimal effective dose of cetuximab to do so.

### Secondary outcome

Secondary endpoints are determination of the ability of plasma from patients treated with cetuximab to induce growth inhibition and antibody-dependent phagocytosis of tumor cells. Additionally, we will determine the level of EGFR expression on CTCs, the immune profile, RAS mutation status and disease free survival.

# Study description

### Background summary

One of the most frequent complications of colorectal cancer is the development of liver metastases, which results in high morbidity and mortality. Previously,

we showed in animal models that abdominal surgery (necessary to remove the tumor) enhances the risk of liver metastases development. This is due to the concomitant inflammatory response, which induces vascular changes in the liver, allowing the adherence of circulating tumor cells (CTCs). Unfortunately, most patients have CTCs at the time of surgery. Moreover, the presence of CTCs is correlated with poor survival of patients with primary colorectal cancer as well as patients with resectable liver metastases. Thus, we hypothesize that also in patients resection of the primary tumor or liver metastases promotes implantation and metastases of CTCs. Importantly, we recently demonstrated that pre-operative anti-tumor monoclonal antibody (mAb) therapy resulted in efficient antibody-dependent phagocytosis of tumor cells by liver macrophages (Kupffer cells). Moreover, mAb therapy prevented outgrowth of liver metastases in animal models. We therefore now propose to pre-operatively treat patients that are scheduled for surgical treatment (with curative intent) of colorectal liver metastases with the anti-epidermal growth factor receptor (EGFR) mAb cetuximab, as EGFR is expressed in up to ~80% of colorectal carcinoma. We anticipate that pre-operative cetuximab therapy will lead to a reduction in the number of CTCs, which may ultimately decrease the risk of (recurrent) metastases development.

## Study objective

The main objective of this study is to determine whether a single neoadjuvant gift of anti-EGFR mAb, administered 48 hours prior to local treatment of colorectal liver metastases, reduces the number of CTCs. Secondary endpoints are determination of the minimal effective dose of cetuximab, the ability of patient plasma samples to induce growth inhibition and antibody-dependent phagocytosis of tumor cells, level of EGFR expression of CTCs, the immune profile, patient RAS mutation status, and disease free survival.

## Study design

We will perform a dose-finding study to establish the lowest dose of cetuximab that effectively removes tumor cells from the circulation. We will conduct this first trial in patients that are scheduled for (surgical) treatment of colorectal cancer liver metastases with curative intent.

## Intervention

Patients will receive a single dose of cetuximab 48 hours prior to surgery in a dose escalating fashion. Starting dose is 50mg/m2 and this will be increased to 100mg/m2, 200mg/m2, and 400mg/m2 in consecutive cohorts depending on whether the minimal effective dose is determined.

## Study burden and risks

Cetuximab is currently widely used in the clinic in e.g. metastatic head and neck squamous cell carcinoma and colorectal carcinoma with a mild to moderate adverse events profile. In these settings cetuximab is used at an initial dose of 400 mg/m2 followed by weekly doses of 250 mg cetuximab per m2. With this treatment schedule, the predominant side effects of cetuximab include skin reactions, which occur in about 80% of patients, hypomagnesaemia which occurs in approximately 10% of patients and infusion-related reactions, which occur with mild to moderate symptoms in about 10% of patients and with severe symptoms in 1% of patients. Side effects of cetuximab in our study are expected to be less frequent and less severe as most patients in our study will be treated with a lower dose, which will be administered only once. As stated above, we hypothesize that eradicating CTCs will ultimately lead to reduced outgrowth of metastasis in colorectal cancer patients. As metastases of colorectal cancer (and all malignancies in general) contribute greatly to morbidity and mortality, reduction of metastases formation greatly benefits cancer patients.

## Contacts

**Public**
Vrije Universiteit Medisch Centrum

De Boelelaan 1117 1117
Amsterdam 1081 HV
NL
**Scientific**
Vrije Universiteit Medisch Centrum

De Boelelaan 1117 1117
Amsterdam 1081 HV
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

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

## Inclusion criteria

- 18 years or older
- informed consent
- Presence of colorectal cancer liver metastases and patient eligible for local treatment of colorectal liver metastases
- open, laparoscopic or percutaneous treatment of liver metastases, including surgical resection radiofrequent ablation, microwave ablation, irreversible electroporation or combinations of these therapies with curative intent.
- no primary tumor in situ
- A population EGFR/EpCAM+ tumor cells (positive for epithelial markers EpCAM and EGFR) detected in the first blood sample with flow cytometry.
- Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, and diaphragm) during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised. Contraception is necessary for at least 6 months after receiving study drug.

## Exclusion criteria

- Chemotherapy (< 4 weeks prior to surgery)
- Evidence of extrahepatic colorectal cancer metastases
- Prior anti-EGFR mAb therapy
- Other currently active malignancy
- Performance status > ASA 3 (American Society for Anaesthesiologists)
- Expected adverse reactions/allergies for study medication
- Mental disorder/unable to give informed consent
- Pregnancy or breast-feeding patients
- Significant skin condition interfering with treatment
- Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug.
- Radiotherapy to the target lesions during study or within 4 weeks of the start of study drug.
- Major surgery within 28 days before start of study drug.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject*s participation in the study or evaluation of the study results.
- Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.
- Blood transfusion during or directly after surgery

# Study design

## Design

| | |
|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Prevention

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 30-01-2017 |
| Enrollment: | 40 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Erbitux |
| Generic name: | Cetuximab |
| Registration: | Yes - NL outside intended use |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 19-09-2016 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 20-07-2017 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO | |

| | |
|---|---|
| Date: | 19-10-2017 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 24-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 05-06-2018 |
| 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 | EUCTR2015-001646-28-NL |
| CCMO | NL57640.029.16 |