# ‘Improving clinical management of colon cancer through CONNECTION, a nation-wide Colon Cancer Registry and Stratification effort.’

No registrations found.

| | |
|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Pending |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON19889

**Source**
NTR

**Brief title**
CONNECTION II

**Health condition**

Colon cancer

### Sponsors and support

**Primary sponsor:** UMC Utrecht
**Source(s) of monetary or material Support:** Alpe d'Huzes

### Intervention

### Outcome measures

**Primary outcome**

Evaluation of the pathological tumour response to neoadjuvant systemic chemotherapy per

CMS subtype in patients with microsatellite stable high risk stage II and stage III colon cancer.

### Secondary outcome

• Evaluation of the radiological tumour response to neoadjuvant systemic chemotherapy per CMS subtype.
• Assessment of prognostic value of pathological and radiological response to neoadjuvant systemic therapy for recurrence free survival (RFS) at three years.
• Assessment of differences in CMS classification before and after neoadjuvant systemic therapy.
• Assessment of pathologic response by Ki-67, Caspase-3 and cystatic-cytotoxic effects on HE-stained tissue slides.
• Evaluation of diagnostic accuracy of ctDNA measurements for monitoring treatment response to neoadjuvant treatment and detection of residual disease.

## Study description

### Background summary

Colorectal cancer is the third most common cancer in the Netherlands with an incidence around 14,500 patients in 2017. Patients with high-risk stage II (defined as T4N0) or III colon cancer routinely undergo surgery with curative intent and are being offered adjuvant chemotherapy to reduce the chance of recurrence of disease, when fit for treatment. Despite this intensive treatment, 20% of the patients with high risk stage II and 30-35% of the patients with stage III colon cancer will still develop metastatic disease. In addition, on estimate, 50% of the patients with high-risk stage II and stage III colon cancer would never develop metastases after surgery and are therefore over-treated with adjuvant chemotherapy. Unfortunately, it is currently not possible to predict and identify the patients who will develop recurrence of disease without adjuvant therapy after surgery and therefore it is not feasible to perform optimal patient selection for adjuvant chemotherapy. The consensus molecular subtypes (CMS) in colorectal cancer, consisting of four molecular subtypes, is currently considered the most robust classification of colorectal cancers with clear distinctive biological features. Although the available evidence does not clearly delineate the predictive and prognostic value of CMS, the biological features of the subtypes and the scarce literature available provide some handles.
First, CMS1 tumours, which are generally MSI and hypermutated, show high response to immunotherapy in metastatic disease. It is quite evident that survival of patients with an MSI tumour is much better compared to patients with MSS tumours and it has also been observed that MSI predicts lack of response to conventional chemotherapy. Therefore, according to the new recommendations of the “Dutch Association of Medical Oncology” (NVMO), the advice is to refrain from adjuvant chemotherapy in patients with an MSI tumour staged as high-risk stage II given that for these patients adjuvant chemotherapy has no clinically relevant benefit. Second, CMS4 tumours, characterized by a mesenchymal phenotype, seem to have a worse prognosis when compared to CMS1-3. This may be due to biological features resulting

in more metastatic potential and/or a poor response to chemotherapy. Roepman et al showed a similar overall survival for patients treated with and without adjuvant chemotherapy for patients with colorectal cancer classified as a mesenchymal phenotype. Last, CMS2 and CMS3 remain subtypes for which the response to chemotherapy is unknown. Recent data indicate that in the adjuvant setting the benefit of oxaliplatin is only observed in a proportion of colon cancers, which predominantly belong to the CMS2 subtype. Combined, these observations provide further support for the idea that subtypes may be used to predict response to therapy. A solid response monitoring per subtype is hard to obtain because differences in prognosis and response to therapy are difficult to segregate in these patients. The FOxTROT Collaborative Group (2012) was the first to set up a trial with neoadjuvant chemotherapy in patients with locally advanced resectable colon cancer and concluded that preoperative chemotherapy is feasible with acceptable toxicity and perioperative morbidity. These observations lead us to propose a study to investigate the role of subtypes on therapy response in a novel neoadjuvant setting that allows to determine therapy efficacy in individual patients and in the different early stage colon cancer subtypes.

**Study objective**

CMC subtypes matter in the therapy response to systemic chemotherapy for patients with high risk stage II and stage III colon cancer

**Study design**

-

**Intervention**

neoadjuvant CAPOX

# Contacts

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# Eligibility criteria

## Inclusion criteria

To be eligible to participate in this study, a subject must meet all the following criteria:

• Histologically proven cT3-4, N0-2, M0 primary colon cancer, patients with rectal cancer will be excluded from this study. If there is uncertainty about the origin of the carcinoma (i.e. colon or rectum), it is up to the local treating physician to decide whether the patient is eligible. For tumours located in the rectosigmoid region, the decision of the local multidisciplinary team will determine if a patient is eligible for this study.
• 18 years
• Patient is able and willing to provide written informed consent for the CONNECTION- study
• Informed consent for PLCRC components 'clinical data', 'tissue' and 'future studies'
• MSS based on pre-treatment biopsy by IHC
• Fit to undergo neoadjuvant chemotherapy with capecitabine + oxaliplatin and subsequent surgery judged by the primary treating physician
• Adequate bone marrow, liver and renal function
- absolute neutrophil count (ANC) ≥1.5 x 109/L
- platelets ≥100 x 109/L
- HB ≥ 5.5 mmol/L
- Total bilirubin ≤ 1.5 UNL
- ASAT ≤ 5 x UNL
- ALAT ≤ 5 x UNL
- alkaline phosphatase ≤ 5 x UNL
- creatinine clearance >30 ml/min

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

• Any other malignant disease within the preceding 5 years apart from non-melanomatous skin cancer, carcinoma in situ and early stage disease with a recurrence risk <5%
• Colonic obstruction that has not been defunctioned by a stoma
• Pregnant or lactating women

# Study design

### Design

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non controlled trial |
| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 19-03-2019 |
| Enrollment: | 260 |
| Type: | Anticipated |

### IPD sharing statement

**Plan to share IPD:** No

## Ethics review

Positive opinion

| | |
|---|---|
| Date: | 07-03-2019 |
| Application type: | First submission |

## 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 |
|---|---|
| NTR-new | NL7567 |
| Other | METC UMC : METC18/712 |

# Study results