# Molecular imaging with radiolabeled bevacizumab in metastatic colon carcinoma; a feasibility study in patients who do not show response on bevacizumab therapy.

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To recognize the distribution pattern of 111In-bevacizumab in patients who do not show response on treatment with bevacizumab. The ultimate goal is to identify and select patients who can be successfully treated.

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON31048

**Source**
ToetsingOnline

**Brief title**
Radiolabeled bevacizumab in resistant patients with colon carcinoma

### Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

**Synonym**
colon cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** KWF,roche (unrestricted grant)

## Intervention

**Keyword:** bevacizumab, colon carcinoma, imaging

## Outcome measures

### Primary outcome

Safety assessments will consist of evaluating laboratory parameters and adverse

events according to NCI CTCAE 3.0

The following variables will be analyzed to assess the effectiveness of

bevacizumab in the treatment of metastatic colon carcinoma:

• Biological parameters.

• 111In-bevacizumab distribution kinetics by gamma-camera imaging. Evaluation

of gamma-camera imaging to recognize the distribution pattern of

111In-bevacizumab in patients who do not show response to bevacizumab therapy.

### Secondary outcome

n.a.

# Study description

### Background summary

1.1 Treatment of metastatic colon rectal carcinoma (CRC)

For a long time, 5-flourouracil (5-FU) has been the only proven treatment for

colorectal cancer. 5-FU treatment was generally combined with leucovorin. Novel cytotoxic agents have expanded the treatment options. New compounds like irinotecan, oxaliplatin and capecitabine have been implicated.
Co-administration of first irinotecan and secondly oxiplatin to 5-FU/leucovorin (FOLFOX-regime) lead to increased patients survival. These data have caused that the FOLFOX regime was approved as first-line chemotherapy for metastatic CRC.
Although these new drugs lead to increased survival, the poor prognosis of metastatic CRC has encouraged the development of new drugs, preferably with minimal toxicity. Recently, new drugs have been developed, targeting different pathways which are known to drive tumor progression. Some of these drugs, like trastuzumab have shown clinical benefit in for example breast cancer.
Another example is bevacizumab (Avastin®) which is a humanized monoclonal antibody designed to inhibit vascular endothelial growth factor (VEGF), the key mediator in angiogenesis. In the first phase III trial, bevacizumab was combined with first line chemotherapy IFL (irinotecan, 5-FU and leucovorin) in the treatment of CRC. Bevacizumab was i.v. administered once every two weeks in a dose of 5 mg/kg. The primary endpoints were significantly increased. The overall survival improved from 15.5 to 20.3 months ($p<0.001$). Patient disease free survival increased from 6.2 to 10.6 months ($p<0.001$). The overall response rate increased from 34.8% to 44.8% ($p=0.004$) in the arm treated with bevacizumab compared to the IFL/placebo arm. This benefit was seen in all patient groups, independently from age, sex, performance status and location of the primary tumor.
In a subgroup analysis of patients, who were given first line IFL/bevacizumab followed by oxaliplatin-based progression therapy a median overall survival of 25.1 months was showed, compared to 19.6 months for patients receiving no oxaliplatin therapy. Preliminary data of second line treatment with FOLFOX and bevacizumab showed increased response from 21.8% versus 9.2% in the FOLFOX/placebo group ($p=0.0001$).
These data suggest that a subset of patients may still benefit from anti-angiogenic treatment in second line therapy, but most patients will have only side-effects.

1.2. Angiogenesis:
There are several factors involved in the development and growth of tumors. Angiogenesis, the forming of new blood vessels is one of these factors. New vasculature allows tumor cells to execute their critical growth by supplying the tumor with nutrients and oxygen, disposal of metabolic waste products and provides route for metastatic spreading. An important factor involved in angiogenesis is VEGF. VEGF is released by tumor cells and induces tumor neovascularization. VEGF consists of at least 4 splice variants, containing 121, 165, 189 and 206 amino acids 7, involved in endothelial proliferation, tubular formation, endothelial survival, endothelial migration, vascular permeability and gene expression. These actions are thought to be transmitted by the VEGF-receptors VEGFR-1, VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4). The VEGF-receptors are tyrosine kinase mediated transmembrane receptors. The VEGF

production is thought to be regulated by hypoxemia, cytokines and cell differentiation.
Over-expression of VEGF occurs in many human tumor types. The local VEGF production leads to paracrine effects in the tumor, resulting in angiogenesis and growth exploration. This has lead to interest in blocking the signaling of VEGF in human tumors. Chemical molecules which can block the tyrosine kinase function of VEGF-receptors and antibodies binding to the ligand and the receptor have been developed.

1.3 Bevacizumab
The monoclonal antibody bevacizumab is derived from the murine VEGF monoclonal antibody A4.6.1. It blocks VEGF induced endothelial cell proliferation, permeability and survival, and it inhibits human tumor cell line growth in nude mice. The likely mechanism of its anti-angiogenic activity is that soluble VEGF is prevented from binding to its receptors, thereby blocking the biological pathways of VEGF.
Bevacizumab is registered for clinical use in metastatic colon carcinoma. It proved to be also promising (in combination with conventional chemotherapy) in patients with NSCLC and breast cancer.

**Study objective**

To recognize the distribution pattern of 111In-bevacizumab in patients who do not show response on treatment with bevacizumab. The ultimate goal is to identify and select patients who can be successfully treated.

**Study design**

Observational study evaluating the feasibility of 111In-bevacizumab in non-responding patients.

Study procedure
Distribution kinetics of 111In-bevacizumab will be evaluated in non-responding patients (see patients and methods) receiving second line/ third chemotherapy. The following procedure will be followed:
• At day 14 of the first chemotherapy cycle (following inclusion in the study protocol) patients will be injected with 111In-bevacizumab.
• Gammacamera imaging will initially be performed at day 0, 2, 4 and 7 days after a single intravenous administration of 150 MBq 111In-bevacizumab (±10 mg protein). (The optimal time to scan the patients will be determined after two or three patients. Hereafter patients will only be scanned once or twice after tracer injection, most likely on day 0 and 4 after tracer injection.)

Planar whole body imaging will be performed, using a two-headed gammacamera, equipped with parallel-hole medium-energy collimators, at a scan speed of 10 cm/min (day 0 and 2 after injection) or 5 cm/min (day 4 and 7 after injection)

and stored digitally in a 256 x 1024 matrix. An aliquot of dose will be scanned simultaneously. Optionally, single photon emission computed tomography (SPECT) will be performed of regions. Per imaging session, the total amount of scan time will not exceed 90 minutes.

50 ml of blood will be drawn before administration of 111In-bevacizumab and before every scan to determine biological parameters in the circulation and levels of 111In-bevacizumab in the circulation. (see paragraph 6.3).

**Study burden and risks**

In this study 111In-bevacizumab is administered in tracer-dose, therefore the risk of pharmacological side-effects is minimized. Although the additional risk of the bevacizumab tracer dose (± 10 mg) administration besides treatment with chemotherapy including bevacizumab therapy (250-400 mg/every 2 weeks) is most likely negligible, it can not be completely excluded.

The most common side-effects reported after first line chemotherapy with bevacizumab therapy are leukopenia, diarrhea, hypertension, thrombotic events, deep thromboplebitis, pulmonary embolus, bleeding, proteinuria and gastro-intestinal bleeding. These events are for the most part mild to moderate in severity and clinically manageable (hypertension, proteinuria, minor bleeding) or occur uncommonly (wound healing complications, GI perforations and arterial thrombosis). Whether or not a tracer dose of 111In-bevacizumab can induce any adverse effect is unknown. Although no toxicity is expected from the tracer-dose, if present, toxicity will be scored according to the Common Toxicity Criteria version 3.0.

Administration of 111In-bevacizumab entails radiation load for the participating patients. It has been calculated that a dose of 150 MBq will lead to a radiation load of 27 mSv (see appendix 13.3). For comparison purposes, a CT-abdomen will lead to a radiation dose of 10-15 mSv. The poor prognosis of this patient group (5 year survival < 8%) and the potential new information given by this study makes this radiation load acceptable.

# 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. Metastatic colon cancer.
2. Progression of disease (RECIST) after chemotherapy including bevacizumab
3. At least 18 years of age.
4. A life expectancy of at least 3 months.
5. Adequate hematologic, hepatic, and renal function.
6. Signed written informed consent.
7. Able to comply with the protocol.

## Exclusion criteria

1.Radiotherapy within 14 days before the start of the study of the involved area.
2.Major surgery within 28 days before the initiation of the study.
3.Clinically significant cardiovascular disease.
4.Pregnant or lactating women. Documentation of a negative pregnancy test must be available for pre-menopausal women with intact reproductive organs and for women less than two years after menopause.
5.CNS metastases (CT-scan not mandatory).
6.Treatment with any investigational drug within 30 days before the start of the study.
7.Prior allergic reaction to immunoglobulins or immunoglobulin allergy.

# Study design

## Design

**Study type:** Observational invasive

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-05-2007 |
| Enrollment: | 6 |
| Type: | Anticipated |

# Ethics review

Approved WMO

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| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# 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 | EUCTR2006-005858-75-NL |
| CCMO | NL17078.042.07 |