# A Randomized, Double-Blind, Multicenter Phase 3 Study of Irinotecan, Folinic Acid, and 5-Fluorouracil (FOLFIRI) Plus Ramucirumab or Placebo in Patients With Metastatic Colorectal Carcinoma Progressive During or Following First-Line Combination Therapy With Bevacizumab, Oxaliplatin, and a Fluoropyrimidine

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

## Summary

### ID

NL-OMON36541

**Source**
ToetsingOnline

**Brief title**
JVBB (219/388)

## Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

**Synonym**
Cancer of the colon and rectum, metastasized cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Eli Lilly
**Source(s) of monetary or material Support:** Eli Lilly and Company

## Intervention

**Keyword:** Carcinoma, Colorectal, Ramucirumab

## Outcome measures

### Primary outcome

Efficacy: Efficacy assessments include imaging studies/tumor assessments, according to RECIST v. 1.1, performed every 6 weeks (±3 days); PRO assessments; serum carcinoembryonic antigen; and survival.

Safety: Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, and clinical laboratory assessments. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA*). Adverse events and clinical laboratory values will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.02 (NCI CTCAE v. 4.02).

### Secondary outcome

Immunogenicity: Serum samples will be analyzed for antibodies to ramucirumab at baseline, on study, and following the last ramucirumab infusion.

Pharmacokinetics: Pharmacokinetic parameters may be analyzed, including, but not limited to, calculation of mean serum peak and trough concentrations (Cmax and Cmin, respectively).

Translational Research: Blood samples will be analyzed for potential pharmacodynamic markers, including, but not limited to, placental growth factor, vascular endothelial growth factor A (VEGF-A), VEGF-C, VEGF-D, soluble vascular endothelial growth factor receptor 1 (VEGFR-1), and soluble VEGFR-2. In addition, whole blood samples will be used for DNA/genotype analysis and will include an examination of, but will not be limited to, VEGFR-2, CXC chemokine receptor 2, intercellular adhesion molecule 1, and VEGF-A. Historical tumor tissue samples will be collected from all patients for an evaluation of tumor-specific mutations and other biomarkers of interest.

Progression-free survival is defined as the time from the date of randomization until the date of objectively determined progressive disease (according to RECIST v. 1.1) or death due to any cause, whichever is first.

The ORR in each treatment group will be compared using the Cochran-Mantel-Haenszel test adjusting for the stratification variables. Exact confidence bounds (confidence interval: 95%) will be determined. The objective response rate (for patients with measurable disease per RECIST v. 1.1) is defined as the proportion of patients with a best overall response of partial response or complete response.

The EORTC QLQ-C30 and EQ-5D will be analyzed using descriptive statistics.

Safety analyses will be performed on all randomized patients who received any quantity of study treatment. Safety evaluation will be performed based on the actual study treatment a patient has received. Adverse events that are considered unrelated to treatment by the investigator and that occur more than 30 days after the decision is made to discontinue study treatment will not be reported or analyzed. Safety analyses will include summaries of the incidence of AEs by maximum CTCAE grade (Version 4.02) that occur during the study treatment period or within 30 days (± 3 days) after the decision is made to discontinue study treatment. Additionally, the following safety-related outcomes will be summarized:

* study treatment discontinuations due to AEs
* deaths during the study treatment period or within 30 days after the decision is made to discontinue study treatment
* serious adverse events during the study treatment period or within 30 days after the decision is made to discontinue study treatment
* hospitalizations and transfusions during the study treatment period or within 30 days after the decision is made to discontinue study treatment

Pharmacokinetics/Pharmacodynamics/Immunogenicity: Serum and/or plasma concentrations of ramucirumab and pharmacodynamic biomarkers, polymorphisms of genes involved in angiogenesis, and incidence of anti-ramucirumab antibodies will be tabulated.

Translational Research: Translational research will be performed to analyze

relevant biomarkers and to correlate them to clinical outcome.

# Study description

### Background summary

Inhibition of angiogenesis is considered a promising approach to the treatment of cancer. Vascular endothelial growth factor (VEGF) family members are important regulators of angiogenesis and VEGF-A (also known as VEGF) has been shown to be an important therapeutic target in advanced colorectal carcinoma (CRC). VEGF is overexpressed in CRC tissue and may be the single most important tumor angiogenic factor.
Disabling the function of the vascular endothelial growth factor receptor-2 (VEGFR-2) signaling pathway via a number of approaches, including anti-VEGF antibodies, anti-VEGFR-2 antibodies, and small molecule tyrosine kinase inhibitors, has been shown to inhibit new blood vessel formation and tumor growth in a variety of animal models. Therapeutic agents that interfere with the function of VEGF and its receptors may represent efficacious approaches to antiangiogenic and antitumor therapy.
Ramucirumab (IMC-1121B, LY3009806) is a recombinant human monoclonal antibody (mAb) that specifically binds to the extracellular domain of VEGFR-2 with high affinity. Phase 1 studies and initial Phase 2 studies investigating ramucirumab drug product (DP) have provided information regarding safety and tolerability at clinically relevant doses, with preliminary evidence of clinical efficacy in a variety of human cancers.
Bevacizumab, a recombinant humanized mAb that selectively inhibits VEGF-A, has demonstrated efficacy in the treatment of metastatic CRC. This approved agent provides proof of concept for the use of ramucirumab DP in metastatic CRC, owing to a similar mechanism of action. Yet, since ramucirumab DP blocks the binding of several VEGF ligands (VEGF-A, VEGF-C, and possibly VEGF-D) to VEGFR 2, its use may be efficacious among patients who have previously had disease progression on a first-line regimen containing bevacizumab.
Recent evidence suggests that patients whose tumors have an activating mutation in KRAS have a poor response to mAbs targeting the epidermal growth factor receptor. Therefore, treatment options for such patients are limited.
Importantly, recent data suggest that the clinical benefit of bevacizumab in metastatic CRC is independent of KRAS mutation status, suggesting that both patients with an activating mutation in KRAS as well as those who are KRAS wild-type may derive benefit from ramucirumab DP.

### Study objective

The primary objective of this study is to compare overall survival (OS) in patients with metastatic colorectal carcinoma (CRC) when treated with FOLFIRI

in combination with placebo versus FOLFIRI in combination with ramucirumab DP.

Secondary objectives are to compare FOLFIRI plus placebo treatment with FOLFIRI plus ramucirumab DP treatment for:
* progression-free survival (PFS)
* objective response rate (ORR)
* patient-reported outcome (PRO) measures (using European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and EuroQol EQ 5D)
* safety profile
* assessment of the association between biomarkers and clinical outcome
In addition, secondary objectives include:
* assessment of anti-ramucirumab antibodies (immunogenicity)
* assessment of serum levels of ramucirumab

**Study design**

This is a randomized, double-blind, placebo-controlled Phase 3 trial in which patients with metastatic CRC who have had disease progression during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine will be randomized to receive either FOLFIRI plus placebo or FOLFIRI plus ramucirumab DP. Approximately 1050 patients (525 patients per treatment arm) will be randomized to observe 756 OS events.

Patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms as follows: FOLFIRI plus placebo every 14 days or FOLFIRI plus ramucirumab DP every 14 days. Randomization will be stratified by geographic region (North America versus Europe versus all other regions), KRAS status (mutant versus wild-type), and time to disease progression after beginning first-line treatment (< 6 months versus > 6 months).

Treatment will continue until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision. Radiological evaluation of disease response will be conducted approximately every 6 weeks (±3 days) from first dose of study treatment until disease progression. Following discontinuation of study treatment, all patients will be followed for survival at regularly scheduled intervals (approximately every 3 months) until death or until the required number of OS events has been observed.

**Intervention**

-Blood and urine samples will be collected for specified standard laboratory tests
-Four blood samples will be collected so that the sponsor can measure the proteins (antibodies) generated by the body*s immune system in response to treatment with ramucirumab.

-A blood sample for plasma will be collected 4 times during the study.
-The sponsor would also like to collect an additional eight blood samples to measure the amount of study drug that is in the body and how the body breaks it down (This is an optional part of the study, which the patient may decline)
-Collection of a colorectal cancer tissue sample is a mandatory part of this study
-chest CT and a CT or MRI of the abdomen and pelvis will be performed
- an ECG will performed

**Study burden and risks**

Very Common Side Effects (At least 10% of patients)
* Nausea.
* Diarrhea.
* Loss of appetite
* Fatigue.
* Headache.
* High blood pressure. Life-threatening high blood pressure has been reported.
* Abnormal bleeding

Furthermore patients might experience discomforts during the study procedures: blood sampling, providing urine, Echocardiogram, Magnetic Resonance Imaging(MRI), CT scan, contrasts for CT scans. Please refer to Appendix 2 of the Patient Information Sheet for more information regarding the possible discomforts of these procedures

# Contacts

**Public**
Eli Lilly

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US
**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Patients will be at least 18 years of age with metastatic CRC progressive during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients may have either measurable or nonmeasurable disease based on the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v. 1.1), and must have Eastern Cooperative Oncology Group status of 0 or 1as well as adequate hematologic, coagulation, and organ function.

## Exclusion criteria

Patients must have received no more than 2 prior systemic chemotherapy regimens in any setting and must not have experienced a Grade 3 or higher bleeding event within 3 months prior to randomization, or an arterial thrombotic event within 12 months of randomization. Patients must also not have an uncontrolled intercurrent illness, leptomeningeal disease or brain metastases, or active infection requiring parenteral therapy. Lastly, patients must not have received bevacizumab within 28 days of randomization.

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |

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| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-02-2012 |
| Enrollment: | 60 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Ramucirumab |
| Generic name: | NA |

## Ethics review

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| Approved WMO Date: | 17-01-2011 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 29-03-2011 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 05-09-2011 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 07-12-2011 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |

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| Approved WMO Date: | 25-04-2012 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 10-05-2012 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 12-06-2012 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 25-06-2012 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 18-12-2012 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 29-01-2013 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 12-06-2013 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 26-05-2014 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 15-07-2014 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |

# 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 | EUCTR2010-021037-32-NL |
| ClinicalTrials.gov | NCT01183780 |
| CCMO | NL34026.096.10 |