# Open-label, Multicentre, Phase Ib/II Study of MEN1611, a PI3K Inhibitor, and Cetuximab in Patients with PIK3CA Mutated Metastatic Colorectal Cancer Failing Irinotecan, Oxaliplatin, 5-FU and Anti-EGFR Containing Regimens

Published: 19-03-2020
Last updated: 14-03-2025

Main objectiveStep 1: To determine the recommended phase 2 dose (RP2D) of MEN1611 when administered orally in combination with cetuximab to patients with PIK3CA mutated colorectal cancer failing irinotecan, oxaliplatin, 5-FU and anti-EGFR containing...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Metastases |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54485

**Source**
ToetsingOnline

**Brief title**
MEN1611-02 C-PRECISE-01

### Condition

- Metastases

**Synonym**
colorectal cancer metastatic colorectal cancer

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Menarini Ricerche S.p.A.
**Source(s) of monetary or material Support:** pharmaceutical industry

## Intervention

**Keyword:** Cetuximab, MEN1611, metastatic colorectal cancer, PIK3 Inhibitor

## Outcome measures

### Primary outcome

Step 1 (Identification of Dose for Cohort Expansion):

1. Identification of the dose for the Cohort Expansion, defined as the highest dose level (maximum dose tested 48 mg BID, minimal dose tested 32 mg BID) at which no more than 1 of 6 patients experiences a Dose limiting toxicity (DLT) during the DLT assessment window (28 days) or the maximum dose judged to be tolerable by the DSC. The DSC will review and evaluate all the available safety data, any DLTs
and PK data collected during Step 1, in order to confirm the RP2D to be tested in Step 2.

Step 2 (Cohort Expansion Phase):

1. Best ORR defined according to RECIST v1.1 assessment locally performed using CT scan or MRI of the chest and abdomen (including pelvis and adrenal glands). Any other areas of disease involvement should be additionally investigated based on signs and symptoms of the individual patient.

### Secondary outcome

1. Safety and tolerability:

-Incidence, severity as per CTCAE version 5.0 grading, seriousness and treatment-causality of treatment emergent adverse events (TEAEs).

-Frequency of clinically significant abnormalities in physical examination, safety laboratory tests, urinalysis, vital signs and 12-lead ECG.

2. PK profile: MEN1611 plasma concentration-time data will be analysed using a population PK approach. A nonlinear mixed effects model will be used to determine population PK parameters and their associated variabilities (e.g. apparent systemic clearance [CL/F], [V/F], [Ka]).

Individual PK parameters (e.g. area under the concentration time curve [AUC], maximum observed plasma concentration [Cmax]) will be estimated using a post hoc analysis.

3. Disease Control Rate (DCR) defined as percentage of patients whose disease shrinks or remains stable over a certain time period. DCR is the sum of the complete, partial and stable disease rates according to local assessment.

4. Duration of response defined as time from confirmation of a (Partial Response) PR, (Complete response) CR or (Stable Disease) SD, as locally assessed, until the disease has been shown to progress following treatment.

5. Progression-free survival (PFS): defined as the number of days between the first study treatment administration to the date of first documented disease progression as per local assessment, relapse or death from any cause. Responding patients and patients who are lost to follow-up are censored at their last tumour assessment date.

6. Overall Survival (OS): Defined as the number of days between the first study treatment administration and death from any cause.

For the baseline assessment, CT scan or MRI should be performed no more than 4 weeks before the start of study treatment. Follow-up assessment will be performed every 2 cycles during study treatment starting from Day 1 Cycle 3 (within a window of 7 days before the visit date) until objective disease progression as defined by RECIST v1.1 or at the End of Study Visit. Any other site at which a new disease is suspected should be appropriately imaged. If an unscheduled assessment is performed and the disease has not progressed, subsequent assessments should be performed at their scheduled visits.

# Study description

**Background summary**

Colorectal Cancer (CRC) is one of the most commonly diagnosed cancer worldwide and a leading cause of death. The prognosis for patients with metastatic CRC (mCRC) is poor. Besides a selected number of local therapies the vast majority of patients with mCRC receive systemic treatment with chemotherapeutic agents such as irinotecan, oxaliplatin, fluropyrimidines, in combination with targeted monoclonal antibodies, such as cetuximab, bevacizumab, panitumumab, aflibercept, and ramucirumab considered to be the currently accepted standard of care for first or second line treatment. However, the optimal chemotherapeutic regimen beyond second line treatment remains unclear and more than 30% of mCRC patients receive 3 or more lines of therapy.

Cetuximab is an EGFR antibody which causes an interruption of EGF-mediated tyrosine kinase signal transduction pathway in order to reduce cellular proliferation. In the last years, several findings directed to the identification of other predictive biomarkers: KRAS and NRAS mutations have been identified as biomarkers of resistance to anti-EGFR antibodies and these antibodies are currently recommended for mCRC patients expressing wild-type RAS.

Phosphoinositide 3-kinases (PI3Ks) control most key regulatory factors in many cellular processes including cell cycle, survival, proliferation and differentiation, metabolism, motility, migration and genomic instability. PI3K is activated by among others EGFR. In most cases of cancer, PI3K shows mutations that lead to hyperactivity increasing cellular proliferation.

Frequently observed mutations are in the phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (PIK3CA) and the PTEN (phosphatase and tensin homolog deleted from chromosome 10) gene.

The RAS/RAF/MEK/ERK and PI3K/AKT/PTEN signaling pathways are strictly connected. EGFR in fact, also triggers the PIK3CA/PTEN signalling cascade and both can be blocked by EGFR inhibitors, causing tumour cell apoptosis.

Treatment options for patients with RAS wild-type, PI3K mutated metastatic colorectal cancer after progression with standard chemo- and targeted therapy including anti-EGFR containing regimens remain poor. Preclinical data suggested that combination therapies directed against both PI3K and EGFR pathways might improve responses in head and neck squamous cell carcinoma (HNSCC). Given these promising data, several clinical studies assessing cetuximab in combination with inhibitors of PI3K have been opened in HNSCC.

Therefore, the current study is designed because rational combination of cetuximab and the PI3K inhibitor MEN1611 should block each possible signaling cascade and represent an optimal approach to overcome anti-EGFR therapy resistance.

**Study objective**

Main objective
Step 1: To determine the recommended phase 2 dose (RP2D) of MEN1611 when administered orally in combination with cetuximab to patients with PIK3CA mutated colorectal cancer failing irinotecan, oxaliplatin, 5-FU and anti-EGFR containing regimens.
Step 2: To assess the anti-tumour activity of MEN1611 in combination with cetuximab in patients with PIK3CA mutated metastatic colorectal cancer failing irinotecan, oxaliplatin, 5-FU and anti-EGFR containing regimens.

Secondary objective
- To assess the safety and tolerability of MEN1611 in combination with cetuximab.
- To assess the (pharmacokinetic) PK profile of MEN1611 when given in combination with cetuximab.

**Study design**

This is an open-label dose-confirmation and cohort expansion, multicentre, Phase Ib/II study. The study will consist of 2 sequential steps:
Step 1 (Confirmation of Dose for Cohort Expansion): The starting dose of MEN1611 will be 48 mg twice daily (BID). If 48 mg BID in combination with cetuximab is established as safe and tolerable in the first 6 DLT evaluable patients treated (i.e. no more than 1 DLT shall be reported at this dose in a

total of n=6 patients), 48 mg will be considered as the recommended Phase 2 dose (RP2D) to be tested into the expansion phase. In case 48 mg BID in combination with cetuximab is considered to be not tolerable a lower dose level of 32 mg BID will be tested in cohort 2. If 32 mg BID is safe and tolerable according to the protocol in the first 6 DLT evaluable patients treated, 32 mg BID is the RP2D to be tested into the expansion phase (i.e. no more than 1 DLT shall be reported at this dose in a total of n = 6 patients). If 32 mg BID in combination with cetuximab will not be tolerated, the study will be stopped and Step 2 will not be initiated.
Step 2 (Cohort Expansion Phase): The RP2D will be tested for efficacy in 40 evaluable patients (considering also patients already included in Step 1).
Step 2 will explore the anti-tumour activity of MEN1611 combined with cetuximab with further assessment of their safety and tolerability.

**Intervention**

The study intervention consists of:
1. MEN1611, oral capsule: 16 mg capsules to be administered twice daily (BID) for a continuous 28-day cycle. Patients will receive MEN1611 either 48 mg or 32 mg BID (as 3 or 2 capsules, respectively), for a total daily dose of 96 mg or 64 mg, respectively.
2. Cetuximab, solution for infusion: a loading intravenous (IV) dose of 400 mg/m2 of cetuximab is administered as a 120 minutes infusion on Day 1 of Cycle 1, followed by weekly IV infusion (60 minutes) of 250 mg/m2 maintenance doses starting on Day 8 of a continuous 28-day cycle. Premedication with dexamethasone and a histamine-1 (H1) receptor antagonist (i.e. d-chlorpheniramine or diphenhydramine) is required prior to cetuximab administration.

**Study burden and risks**

In a pharmaceutical trial like this one, every risk or side effect cannot be predicted. Each person*s reaction to a test drug may be different. This is not the first time MEN1611 is being given to humans. In a previous trial, MEN1611 was studied in 38 participants with advanced solid tumors for which there was no standard treatment available. The results of that study suggested that MEN1611 is well tolerated (does not cause serious side effects or discomfort) for total daily doses of up to 96 mg given once a day or divided into 2 daily doses. Most participants had some side effects, including commonly nausea, vomiting, diarrhoea, stomatitis, abdominal pain, dry skin rash, decreased appetite, increased blood sugar leels, anemia, liver disorders, lower airways, and other infections, and fatigue. Cetuximab has been approved by regulatory health authorities and is used by doctors to treat participants with colorectal cancer. However, just like any other medication, cetuximab may have some expected or unexpected side effects, including infusion-related side effects, side effects concerning the skin and the lungs.

At this point, it is not known whether taking MEN1611 in combination with cetuximab may cause worsening of any known side effects or possible unknown effects. However, given the lack of standard therapeutic options for the selected patient population, the pharmacological properties and acceptable toxicological profile shown in preclinical and clinical studies, the risk-benefit assessment is considered favorable in the context of this clinical study.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

Patients meeting all the following criteria will be eligible for entry into the pre-screening: 1. Able to give written informed consent. 2. Metastatic colorectal cancer (mCRC). 3. Progression or recurrence following prior anti-EGFR containing regimen and at least in second line of treatment for mCRC.

4. Known N-K-RAS (exons 2, 3 and 4) wildtype status. 5. Known BRAF wild-type or unknown BRAF status. 6. Male and female aged >= 18 years.

Patients meeting all the following criteria at Screening Visit will be eligible for entry into the study:
1. Able to give written informed consent before any study related procedure.
2. Histological documentation of adenocarcinoma of the colon or rectum with radiological evidence of progressive disease after last treatment received.
3. Progression or recurrence following prior irinotecan, oxaliplatin, fluoropyrimidine containing regimen and anti-(epidermal growth factor receptor) EGFR containing regimens for metastatic disease. Patients who have a history of intolerance of irinotecan-based therapy or who are ineligible to receive irinotecan are also eligible as long as they have received a prior oxaliplatin-based therapy. Patients who have a history of intolerance of oxaliplatin-based therapy or who are ineligible to receive oxaliplatin are also eligible as long as they have received a prior irinotecan-based therapy.
4. Best response according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria to the last anti-EGFR containing regimen of partial response (PR) or at least stable disease (SD) for 4 months.
5. Measurable disease according to RECIST criteria, version 1.1.
6. Having a tumour N-K-RAS (exons 2, 3 and 4) and BRAF wild-type and PIK3CA mutation, as per centrally-analysed ctDNA during the [pre]-screening period using a validated test.
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8. Life expectancy >= 12 weeks.
9. Adequate cardiac function as defined by left ventricular ejection fraction of >= 50% measured by a multigated acquisition (MUGA) scan or echocardiography (ECHO).
10. Adequate bone marrow function as defined by absolute neutrophil count (ANC) of >= 1.5x 10^9/L, platelet count of >= 100.0x 10^9/L and haemoglobin of >= 9 g/dL.
11. Adequate liver function, as determined by total bilirubin within upper limit of normal (ULN) (<= 1.5x ULN if documented liver involvement; <= 3x ULN with direct bilirubin <= 1.5x ULN in case of patients with coexisting known Gilbert's disease) and/or AST and alanine aminotransferase (ALT) <= 2.5x ULN (<= 5x ULN if liver metastases).
12. Adequate renal function assessed by creatinine clearance >= 50 mL/min.
13. Adequate electrolytes (serum potassium and magnesium levels within institutional normal limits). Replacement treatment to achieve adequate electrolytes levels is allowed.
14. Not pregnant, not breastfeeding, and least 1 of the following conditions applies: a) Not a woman of childbearing potential (WOCBP).
OR
b) A WOCBP who agrees to use highly effective contraception 4 weeks before the first dose of the study treatment, during the treatment period and for 6 months following the last dose of the study treatment. Patients should not breastfeed during and at least for 6 months after the last dose of the study treatment.
15. Male patient who is surgically sterile or male patient who is willing to

agree and have his female partners (if WOCBP) agreeing with the true abstinence (refrain from heterosexual intercourse) or who agrees to use and to have his female partners (if WOCBP) using barrier contraceptive measures during the entire study treatment period and for 6 months after the last administration of study drug, and agrees to refrain from donating sperm during the entire study treatment period and for 6 months after the last administration of study treatment.

## Exclusion criteria

Patients will not be eligible for entry into the pre-screening if they meet ANY of the following exclusion criteria: 1. Patients with a known PIK3CA WT status Note: this exclusion criterion does not apply if PIK3CA WT status was assessed before the last anti-EGFR containing regimen. 2. Previous treatment with PI3K inhibitor. 3. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations. 4. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity.

None of the following exclusion criteria shall be met at Screening Visit and will be re-checked at Day 1 Cycle 1:
1. Previous treatment with PI3K inhibitor.
2. Hypersensitivity and/or contraindication to MEN1611, cetuximab or to any component of the formulations.
3. Inability to swallow oral medications.
4. Brain metastases, with the exception of patients with previously treated brain metastases (including radiation and/or surgery) > 4 weeks before the Screening Visit and only if clinically stable (as determined by the Investigator) and not receiving corticosteroids.
5. NCI CTCAE v5.0 Grade >= 2 diarrhoea, which is not resolved in the week prior to the start of the study treatment (Day 1 of Cycle 1, as applicable).
6. History of significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
a) Myocardial infarction within 6 months prior to the first dose of any study treatment (Day 1 of Cycle 1, as applicable).
b) Acute coronary syndromes (including unstable angina, coronary artery bypass grafting [CABG], coronary angioplasty or stenting) within 6 months prior to first dose of any study treatment (Day 1 of Cycle 1, as applicable).
c) Congestive heart failure (CHF) New York Heart Association Class IIIIV.
d) Clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the Investigator.
e) Long QT syndrome or other risk factors for "Torsades de Pointes" or increased QTc interval according to Fridericia formula (QTcF > 450 msec for males and QTcF > 460 msec for females).
f) Ventricular arrhythmia.
7. Symptomatic thromboembolic events or cerebrovascular accident including

transient ischaemic attack within 6 months prior to the start of any study treatment (Day 1 of Cycle 1, as applicable).
8. Uncontrolled hypertension (defined as persistent BP of >= 150/90 mmHg despite treatment, measured on at least 2 separate occasions).
9. Known active or uncontrolled pulmonary dysfunction.
10. Any serious and/or unstable pre-existing psychiatric or neurologic illness or other conditions that could interfere with patient's safety.
11. Uncontrolled diabetes mellitus (HbA1c > 7%) and FPG > 126 mg/dL.
12. Known history of human immunodeficiency virus (HIV) infection or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV).
13. Patients diagnosed with another primary malignancy, except for: adequately treated nonmelanoma skin cancer or cervical cancer in situ; or patients with another primary malignancy who are definitively relapse-free for at least 3 years since the diagnosis of the other primary malignancy.
14. Concurrent chronic immunosuppressive treatment either with steroids or other immunosuppressive agents.
15. Any chemotherapy, radiotherapy, immunotherapy, major surgery, biologic therapy or any other investigational agent within 28 days of the first administration of the study treatment or within five times the half-life of the investigational agent, whichever is longer. Note: Patients may receive palliative radiotherapy for painful bone metastases, as long as <= 25% of the bone marrow was irradiated and does not affect target and non-target lesions being assessed. (Please see section 8.4.8.)
16. Any other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol.
17. Patient receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A as well as strong inhibitoris or inducers of CYP1A within a period corresponding to five times the half-five of the drug prior to the first administration of MEN1611. Switching to a different medication is allowed.
18. Pregnant or breastfeeding women.
19. Inability or unwillingness to abide by the study protocol; legal incapacity or limited legal capacity.
20. Warfarin sodium therapy or any other coumadin-derivative anticoagulant.

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 15-07-2020 |
| Enrollment: | 5 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Erbitux |
| Generic name: | Cetuximab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | NA |
| Generic name: | MEN1611 |

## Ethics review

Approved WMO

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|---|---|
| Date: | 19-03-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 15-07-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

Approved WMO

| | |
|---|---|
| Date: | 30-10-2020 |
| Application type: | Amendment |

| | |
|---|---|
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-11-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 30-11-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 22-02-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 22-04-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-04-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 14-05-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO | |

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|---|---|
| Date: | 31-10-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 03-11-2021 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-01-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 15-02-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 22-08-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# 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 | EUCTR2019-003727-38-NL |
| CCMO | NL72727.056.20 |