TARGET-EU: Clinical benefit of bevacizumab in metastatic colorectal cancer

First published: 11/05/2026

Last updated: 11/05/2026

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000996

Study ID

1000000996

DARWIN EU® study

No

Study countries

Netherlands

Study description

This case study is part of the broader TARGET EU project (EUPAS1000000539), which aims to advance the regulatory use of real-world data through the application of target trial emulation and estimand methodologies.

Background: Colorectal cancer (CRC) is the second most commonly diagnosed type of cancer in women and third most commonly diagnosed type in men, with an incidence of 73.5 per 100,000 inhabitants-year in 2022 in the European Union. The mortality in that year was 32.3 per 100,000 inhabitants. In the Netherlands, 23% of the patients with colon cancer and 19% of the patients with rectal cancer presented with metastatic colorectal cancer (mCRC) at diagnosis. Guidelines recommend fluoropyrimidine-based chemotherapy in combination with oxaliplatin or irinotecan for first-line initially unresectable mCRC. The addition of bevacizumab, an anti-Vascular Endothelial Growth Factor (VEGF) antibody, improved prognosis compared to chemotherapy alone. A randomised clinical trial (RCT) found that addition of bevacizumab had a median overall survival (OS) of 9.4 months compared to 8.0 months for placebo (HR, 0.83; 97.5% CI, 0.72 to 0.95), in combination with oxaliplatin-based chemotherapy.

Objectives: The acceptance of bevacizumab in mCRC treatment landscape varies largely throughout the Netherlands, presumably due to differences in policy and attitude. This study will evaluate the comparative effectiveness of first-line addition of bevacizumab to the capecitabine-oxaliplatin (CapOx) regimen versus the CapOx regimen alone, in initially unresectable mCRC patients.

Methods: We will use the Netherlands Cancer Registry (NCR), a nationwide, population-based, Dutch cancer registry. The primary analysis uses a Cox proportional hazards model, with supplemental analyses using an accelerated failure time model to estimate restricted mean survival time (RMST) at 52 weeks and 104 weeks. Sensitivity analyses will be conducted to assess the impact of censoring assumptions.

Study status

Ongoing

Research institutions and networks

Institutions

Electronic Health Records (EHR) Research Group, London School of Hygiene & Tropical Medicine (LSHTM)

United Kingdom

First published: 19/04/2010

Last updated: 30/10/2024

Institution | Educational Institution | ENCePP partner

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 27/05/2026

Institution | Educational Institution | ENCePP partner

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Prospective Dutch CRC Cohort

Networks

Vaccine monitoring Collaboration for Europe (VAC4EU)

- Belgium
- Denmark
- Finland
- France
- Germany
- Italy
- Netherlands

Norway

Spain

United Kingdom

First published: 22/09/2020

Last updated: 22/09/2020

Network | Outdated | ENCePP partner

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

First published: 01/02/2024

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Network

Contact details

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Study timelines

Date when funding contract was signed
Actual: 19/09/2024

Study start date
Actual: 09/03/2026

Data analysis start date
Actual: 16/03/2026

Date of final study report
Planned: 10/06/2026

Sources of funding

- EMA

Study protocol

Emulation_Protocol_CS10_REV4_clean.pdf (839.43 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

This study will emulate a hypothetical target trial using a retrospective, active-comparator, new-user cohort design based on routinely collected health records.

Main study objective:

The overall aim is to assess progression-free survival (PFS) in patients with mCRC when treated with CapOx-B compared with CapOx alone.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

BEVACIZUMAB

Anatomical Therapeutic Chemical (ATC) code

(L01FG01) bevacizumab

bevacizumab

Medical condition to be studied

Colorectal cancer metastatic

Population studied

Short description of the study population

The study population will consist of adults with metastatic colorectal cancer who initiate treatment with a regimen consisting of capecitabine and oxaliplatin (CapOx), either with or without bevacizumab, during the study period. Cohort

entry (index date) will be defined as the date of treatment initiation (CapOx or CapOx-B).

To be eligible, individuals must:
* have histologically confirmed metastatic colorectal cancer (mCRC)
* be aged 18 years or older at cohort entry.
* have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤ 1
* not have had prior systemic therapy for mCRC or previous treatment with bevacizumab and/ or oxaliplatin,
* not have had radiotherapy or surgery for mCRC within 4 weeks prior to time 0.

No exclusion criteria will be applied.

Age groups

- **Adult and elderly population (≥18 years)**
  - Adults (18 to < 65 years)
    - Adults (18 to < 46 years)
    - Adults (46 to < 65 years)
  - Elderly (≥ 65 years)
    - Adults (65 to < 75 years)
    - Adults (75 to < 85 years)
    - Adults (85 years and over)

Study design details

Setting

This study is conducted using routinely collected electronic health records from 2021 to 2024, reflecting the period of bevacizumab use in routine clinical practice. The study is set in secondary care, drawing on longitudinal cancer registry data from the NCR. Data are sourced from the Netherlands, providing nation-wide, population-based and representative coverage of real-world clinical care.

Comparators

The comparator group consists of patients who initiate the a regimen consisting of capecitabine and oxaliplatin (CapOx regimen).

The acceptance of bevacizumab in mCRC treatment landscape varies largely throughout the Netherlands, presumably due to differences in policy and attitude.

The use of an active comparator is the most appropriate approach because it aligns with real-world clinical practice and helps to address confounding by indication. It allows for the effectiveness of bevacizumab addition (to the CapOx regimen) to be benchmarked against the CapOx regimen alone.

Outcomes

The primary endpoint will be time to first occurrence of disease progression or death. In the NCR, disease progression is marked by the end of a so-called "episode". An “episode” is defined as the clinical trajectory of a patient up until disease progression.

Data analysis plan

The analyses are conducted within a target trila emulation framework to estimate the effect of the CapOx-B regimen compared with the CapOx regimen

on progression-free survival (PFS).
For Estimand 1, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to first disease progression or death, estimated using a (1:1 matched or inverse probability of treatment weighted (IPTW)) Cox proportional hazards model.

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW), tipping point analysis, and probabilistic bias analysis for non-differential outcome misclassification.

Two supplemental estimands are also defined: Estimand 2, applying a hypothetical and composite strategy for intercurrent events, and Estimand 3, estimating treatment effects using restricted mean survival time (RMST) derived from an IPTW-weighted Weibull accelerated failure time (AFT) model. In addition, supplemental analyses (e.g., crude and IPTW-adjusted Kaplan-Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, covariate balance before and after weighting, censoring and intercurrent event patterns, proportional hazards diagnostics, positivity checks, and multiple-imputation diagnostics) will be conducted to support interpretation of the main analysis.

Summary results

Not yet available

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Netherlands Cancer Registry

Use of a Common Data Model (CDM)

CDM mapping

No

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

v5.4

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation details

The feasibility assessment for this case study, detailed in the appendix of the study protocol, was conducted as part of the broader TARGET-EU feasibility assessment (EUPAS1000000791). Data source suitability was evaluated using a structured framework based on the EMA data quality framework, assessing system characteristics, data quality, and fitness for the research question.

Briefly, the NCR was deemed a feasible data source for studying CapOx(-B) and PFS, with achievable sample sizes and reasonably up-to-date data. The database provides reliable in- and outpatient hospital data and timely updates, but some limitations were identified. For instance, PFS is not captured in the NCR through medical imaging directly, but through a validated algorithm that

marks the end of “episodes”, as previously discussed. The missingness in ECOG PS will not have much impact, since ECOG PS is one of the inclusion criteria.

Data characterisation results

Feasibility assessment CS10.pdf

English (317.87 KB - PDF)

View document