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A randomized, open-label phase 3 study of amivantamab and mFOLFOX6 or FOLFIRI versus cetuximab and mFOLFOX6 or FOLFIRI as first-line treatment in participants with KRAS/NRAS and BRAF wild-type unresectable or metastatic left-sided colorectal cancer

Submission date 17/08/2024	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 29/10/2024	**Overall study status** Ongoing	
Last Edited 14/03/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Kirsten rat sarcoma virus (KRAS), neuroblastoma rat sarcoma virus (NRAS), and v-Raf murine sarcoma viral oncogene homolog B1 (BRAF wild-type colorectal cancer includes a subtype of colorectal cancers (CRCs), defined by the absence of specific genetic alterations*. If this is cannot be removed by surgery and/or has spread to other organs & started in the left side of colon and/or rectum, initial treatment usually includes chemotherapy along with lab-made proteins that can bind to specific targets in the body. One of these proteins is called cetuximab.
*Changes in genes that control the way cells grow and multiply Amivantamab is a bispecific antibody** that targets the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) proteins. It binds to EGFR and MET & turn it off, which may kill or slow down the growth of cancer cells.
**Antibody is a protein that helps protect the body against foreign matter.

In this study researchers want to learn if amivantamab in combination with the chemotherapy treatments (mFOLFOX6 or FOLFIRI) works at slowing the progression of cancer compared to using cetuximab with the same chemotherapy treatments.

Who can participate?
Male & female participants 18 years or older with colorectal cancer.

What does the study involve?
The study will be conducted as follows: -
• Screening Phase (up to 28 days)
• Treatment Phase (until 30 days after stopping the study treatment)- Eligible participants will

be randomly (by chance) assigned to either of the 2 groups:
• Arm 1: Amivantamab and mFOLFOX6 or FOLFIRI
• Arm 2: Cetuximab and mFOLFOX6 or FOLFIRI
• Follow-up Phase (until end of study)- Participants will be followed-up to monitor their health.

Participants will undergo study assessments such as blood, urine tests & questionnaires. Blood samples will be taken at multiple timepoints to understand how the body responds to study treatment. All side effects will be recorded till the study ends. Overall duration of the study will be
up to 4 years and 2 months (approximately).

What are the possible benefits and risks of participating?
There is no established benefit to participants of this study. Based on scientific theory, taking amivantamab may improve colorectal cancer. However, this cannot be guaranteed because amivantamab is still under investigation as a treatment and it is not known whether amivantamab will work.
Participants may experience some benefit from participation in the study that is not due to receiving study drug, but due to regular visits and assessments monitoring overall health. Participation may help other people with colorectal cancer in the future.
Participants may have side effects from the drugs or procedures used in this study that may be mild to severe and even life-threatening, and they can vary from person to person. The most common, known risks are getting symptoms such as skin toxicities, respiratory toxicities, allergic and anaphylactic-like reactions (severe life-threatening allergic reaction) and hypersensitivity (exaggerated immune response to a drug or other substance), infusion reactions, blood-related toxicities, inflammation of the mucosa (membranes that line mouth and gastrointestinal tract), nausea, or vomiting, nervous system related toxicities due to oxaliplatin, and diarrhea (due to irinotecan) after getting the study drug. There are other, less frequent risks. The participant information sheet and informed consent form, which will be signed by every participant agreeing to participate in the study, includes a detailed section outlining the known risks to participating in the study.

Not all possible side effects and risks related to amivantamab are known at this moment. During the study, the sponsor may learn new information about amivantamab. The study doctor will tell participants as soon as possible about any new information that might make them change their mind about being in the study, such as new risks.

To minimise the risk associated with taking part in the study, participants are frequently reviewed for any side effects and other medical events. Participants are educated to report any such events to their study doctor who will provide appropriate medical care. Any serious side effects that are
reported to the sponsor are thoroughly reviewed by a specialist drug safety team

There are no costs to participants to be in the study. The sponsor will pay for the study drug and tests that are part of the study. The participant will receive reasonable reimbursement for study related costs (e.g., travel/parking costs).

Where is the study run from?
Janssen-Cilag International N.V. (Netherlands)

When is the study starting and how long is it expected to run for?
August 2024 to December 2026

Who is funding the study?
Janssen-Cilag International N.V. (Netherlands)

Who is the main contact?
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Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2024-513852-13

Integrated Research Application System (IRAS)
1010643

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
61186372COR3001, CPMS 63168

Study information

Scientific Title

A randomized, open-label phase 3 study of amivantamab and mFOLFOX6 or FOLFIRI versus cetuximab and mFOLFOX6 or FOLFIRI as first-line treatment in participants with KRAS/NRAS and BRAF wild-type unresectable or metastatic left-sided colorectal cancer

Acronym
OrigAMI-2

Study objectives
The primary objective of the study is to compare progression-survival (PFS) in participants treated with amivantamab plus mFOLFOX6 or FOLFIRI versus cetuximab plus mFOLFOX6 or FOLFIRI.

The secondary objectives for the study are (in participants treated with amivantamab plus mFOLFOX6 or FOLFIRI versus cetuximab plus mFOLFOX6 or FOLFIRI):
2.1. To further assess additional measures of clinical benefit
2.2. To assess safety
2.3. To assess disease symptoms, treatment tolerability, and health-related quality of life (HRQoL)

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 28/10/2024, North West - Greater Manchester South Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048065; gmsouth.rec@hra.nhs.uk), ref: 24/NW/0275

Study design
Interventional randomized parallel group controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Unresectable or Metastatic Left-sided Colorectal Cancer

Interventions
• Screening Phase (up to 28 days)
• Treatment Phase (until 30 days after stopping the study treatment)- Eligible participants will be randomly (by chance) assigned to either of the 2 groups:
• Arm 1: Amivantamab and mFOLFOX6 or FOLFIRI
• Arm 2: Cetuximab and mFOLFOX6 or FOLFIRI
• Follow-up Phase (until end of study)- Participants will be followed-up to monitor their health. Participants will undergo study assessments such as blood, urine tests & questionnaires. Blood samples will be taken at multiple timepoints to understand how the body responds to study treatment. All side effects will be recorded till the study ends. Overall duration of the study will be up to 4 years and 2 months (approximately).

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Amivantamab SC, cetuximab

Primary outcome(s)
Progressions-free survival (PFS) (using RECIST v1.1), as assessed by Blinded Independent Central Review (BICR) from randomisation until the date of objective disease progression or death (due to any cause), whichever comes first

Key secondary outcome(s))
Measured using patient records between study treatments:
1. Overall survival (OS).
2. Objective response rate (ORR), as assessed by BICR.
3. PFS and ORR, as assessed by investigator.
4. Duration of response (DoR), as assessed by BICR and investigator.
5. PFS2 (PFS after first subsequent therapy).
6. Disease control rate (DCR), as assessed by BICR and investigator.
7. Time to treatment failure.
8. Curative resection rate.
9. Incidence and severity of adverse events (AEs) and laboratory abnormalities.
10. Change from baseline and time to worsening in symptoms and functioning, as measured by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-CR29.
11. Treatment group differences in overall side effect burden, as measured by EORTC item 168.

Completion date
23/12/2026

Eligibility

Key inclusion criteria
1. Be at least 18 years of age at the time of informed consent.
2. Have histologically or cytologically confirmed adenocarcinoma of the left-sided colorectal cancer (CRC), as specified within the study protocol. Participants must have unresectable or metastatic disease.
3. Be diagnosed to have Kirsten rat sarcoma viral oncogene (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and v-raf murine sarcoma viral oncogene homolog B (BRAF) wild-type (WT) tumour, as determined by local testing.
4. Must agree to the submission of fresh tumour tissue.
5. Have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. If only 1 measurable lesion exists, it may be used for the screening biopsy as long as baseline tumour assessment scans are performed equal to or more than 7 days after the biopsy.
6. Has not received any prior systemic therapy for unresectable or metastatic CRC. Following prior adjuvant/neoadjuvant therapy in the non-metastatic disease is permitted. However, the last course of adjuvant or neoadjuvant chemotherapy must have concluded more than 12

months prior to CRC recurrence/metastases.
7. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.
8. Have at least 1 of the following:
a. Serum creatinine less than or equal to 1.5 times upper limit of normal (ULN).
b. Estimated glomerular filtration rate (eGFR) based on the Modified Diet in Renal Disease (MDRD) 4-variable formula or directly measured creatinine clearance equal to or more than 50 millilitres per minute.
9. Participants must meet the protocol specified hepatic function requirements.
10. Participants must meet the protocol specified hematologic function requirements.
11. While on study treatment and for 9 months after the last dose of study treatment, a participant must not breastfeed or be pregnant, not donate gametes (i.e., eggs or sperm) or freeze for future use for the purposes of assisted reproduction, and must also wear an external condom.
If the participant is of childbearing potential, they must:
a. Have a negative highly sensitive (e.g., beta-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and within 24 hours before randomisation and agree to further pregnancy tests as per the protocol schedule; and
b. Practice at least 1 highly effective method of contraception; if oral contraceptives are used, a barrier method of contraception must also be used.
If a participant's partner is of childbearing potential, the partner must practice a highly effective method of contraception unless the participant is vasectomised.
12. Must sign an Informed Consent Form (ICF; or their legally designated representative must sign) indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.
13. Be willing and able to adhere to the lifestyle restrictions specified in this protocol.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Uncontrolled illness, including but not limited to the conditions specified in the protocol.
2. Medical history of (non-infectious) interstitial lung disease (ILD)/pneumonitis/pulmonary fibrosis, or has current ILD/pneumonitis, or suspected ILD/pneumonitis/pulmonary fibrosis cannot be ruled out by imaging at screening.
3. Has known allergies, hypersensitivity, or intolerance to excipients of amivantamab, cetuximab, any component of mFOLFOX6 (participants receiving mFOLFOX6), or any component of FOLFIRI (participants receiving FOLFIRI).
4. Participant has a history of clinically significant cardiovascular disease, as specified in the study protocol.

5. Has or will have any of the following:
a. An invasive operative procedure with entry into a body cavity within 4 weeks or without complete recovery before the first administration of study treatment (see protocol specified exclusions).
b. Significant traumatic injury within 3 weeks before the start of the first administration of study treatment (all wounds must be fully healed prior to Day 1).
c. Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study treatment.
Note: Port placement for chemotherapy administration is allowed.
6. Has a prior or concurrent second malignancy other than the disease under study or one whose natural history or treatment is unlikely to interfere with any study endpoints of safety or the efficacy of the study treatment(s). Prior or concurrent second malignancies must be reviewed and agreed to with the medical monitor.
7. Participant with known mismatch repair deficiency (dMMR)/ high microsatellite instability (MSI-H) status.
8. Participant with known Receptor tyrosine-protein kinase erbB-2 (HER2) -positive/amplified tumour.
9. Has prior exposure to any agents that target epidermal growth factor (EGFR) or mesenchymal epithelial transition (MET) (including but not limited to protein products, monoclonal antibodies, tyrosine kinase inhibitors, or antisense oligonucleotide therapy).
10. Participant with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
11. Participant who are to receive FOLFIRI must meet additional protocol specific disease characteristics.
12. Has symptomatic or untreated brain metastasis.
13. Has medical history or known presence of leptomeningeal disease or spinal cord compression.
14. HIV-positive participants are not eligible if they meet any of the specific protocol criteria.
15. Has active hepatitis of infectious origin at screening.
16. Had radiation therapy within 28 days before randomisation.
17. Requires a prohibited medication that cannot be discontinued, substituted, or temporarily interrupted during the study.
18. Received an investigational treatment (including investigational vaccines but not including anticancer therapy) or used an invasive investigational medical device within 8 weeks of randomisation.
19. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments.

Date of first enrolment
21/10/2024

Date of final enrolment
23/12/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Belgium

Brazil

Canada

China

France

Germany

Hungary

India

Israel

Italy

Japan

Malaysia

Netherlands

Poland

Spain

Sweden

Taiwan

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Sponsor information

Organisation
Janssen-Cilag International NV

Funder(s)

Funder type
Industry

Funder Name
Janssen-Cilag International N.V.

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing policy of the Janssen Pharmaceutical Companies of Johnson & Johnson is available at www.janssen.com/clinicaltrials/ transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at yoda.yale.edu

IPD sharing plan summary

Available on request