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A randomized, open-label phase 3 study of amivantamab + FOLFIRI versus cetuximab /bevacizumab + FOLFIRI in participants with KRAS/NRAS and BRAF wildtype recurrent, unresectable or metastatic colorectal cancer who have received prior chemotherapy

Submission date 13/09/2024	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 06/11/2024	**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), & v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) wild-type metastatic colorectal cancer are subtypes of colorectal cancers (CRCs), defined by absence of specific genetic alterations*. If cancer cannot be completely removed with surgery &/or has spread to other organs, treatment includes chemotherapy along with lab-made proteins that can bind to specific targets in body, however CRC can return after treatment.
*Changes in genes that control the way cells grow & multiply.
Amivantamab is a bispecific antibody** that binds to the epidermal growth factor receptor (EGFR) & mesenchymal-epithelial transition (MET) proteins & turn them off, which may kill or slow down the growth of cancer cells.
**Protein that helps protect the body against foreign matter.
In this study researchers want to learn if amivantamab in combination with chemotherapy (FOLFIRI) works at slowing the progression of cancer and increase duration of life compared to using cetuximab or bevacizumab with the same chemotherapy, if cancer has returned after initial chemotherapy.

Who can participate?
Participants 18 years or older with colorectal cancer who have previously received chemotherapy.

What does the study involve?
Study will consist of:
• Screening Period (up to 28 days)

• Treatment Period (until EOT/30 days after stopping study treatment): Eligible participants will be randomly (by chance) assigned to either of 2 groups:
o Arm 1: Amivantamab as injection under skin and FOLFIRI injected directly into a vein using a needle.
o Arm 2: Cetuximab or bevacizumab and FOLFIRI injected directly into a vein using a needle.
• Follow-up Phase (until end of study)- Participants will be followed-up to monitor their health.
Participants will undergo study assessments such as blood and urine tests & questionnaires. Blood samples will be taken at multiple timepoints to understand how body responds to study treatment.
All side effects will be recorded till study ends (approximately 2 years 9 months).

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, scarring of lung tissue/inflammation of lung tissue, surgery and wound healing complications, inflammation of the mucosa (membranes that line mouth and gastrointestinal tract), nausea, or vomiting, gastric system related toxicities, excessive loss of blood, cardiovascular system related toxicities, neurological toxicities, excessive protein in urine (due to bevacizumab) 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 NV (Netherlands)

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

Who is funding the study?
Janssen-Cilag International NV (Netherlands)

Who is the main contact?
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Clinical Trials Information System (CTIS)

2024-513853-66

Integrated Research Application System (IRAS)
1010712

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
61186372COR3002, CPMS 63487

Study information

Scientific Title
A randomized, open-label phase 3 study of amivantamab + FOLFIRI versus cetuximab /bevacizumab + FOLFIRI in participants with KRAS/NRAS and BRAF wildtype recurrent, unresectable or metastatic colorectal cancer who have received prior chemotherapy

Acronym
OrigAMI-3

Study objectives
Main objectives
1. To compare how long a participant is disease-free (progression-free survival) and the length of time until a participant dies (overall survival) in participants treated with amivantamab + FOLFIRI versus those treated with cetuximab or bevacizumab + FOLFIRI.

Secondary objectives
1. To further assess additional measures of clinical benefit
2. To assess safety
3. To assess disease symptoms, treatment tolerability (how well participants are managing any treatment related side effects), and how the treatment is affecting their overall quality of life.

Ethics approval required
Ethics approval required

Ethics approval(s)
notYetSubmitted, TBC, ref: 24/SC/0314

Study design
Interventional randomized parallel group controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Recurrent, unresectable or metastatic 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 FOLFIRI
• Arm 2: Cetuximab or bevacizumab and 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 3 years (approximately).

Intervention Type
Drug

Phase
Phase III

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

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

Key secondary outcome(s))
1. Objective response rate (ORR), as assessed by BICR
2. PFS and ORR, as assessed by investigator
3. Duration of response (DoR), as assessed by BICR and investigator
4. PFS2 (PFS after first subsequent therapy)
5. Disease control rate (DCR), as assessed by BICR and investigator
6. Time to treatment failure
7. Curative resection (R0) rate
8. Incidence and severity of adverse events (AEs) and laboratory abnormalities
9. 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
10. Treatment group differences in overall side effect burden, as measured by EORTC item 168

Completion date
14/11/2026

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 colon or rectum.

3. Be diagnosed to have KRAS, NRAS, and BRAF WT tumour as determined by local testing.
4. Agree to the submission of fresh or archival tumour tissue post-progression from the most recent therapy, if clinically feasible.
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. Participant must have received 1 line of systemic therapy for metastatic colorectal cancer (mCRC), with documented radiographic disease progression on or after this line of therapy.
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 equal to or less than 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 6months 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.
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 the 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. Has medical history of (non-infectious) interstitial liver disease (ILD)/pneumonitis/pulmonary fibrosis or has current ILD/pneumonitis/pulmonary fibrosis, or where suspected ILD/pneumonitis /pulmonary fibrosis cannot be ruled out by imaging at screening.

3. Has known allergies, hypersensitivity, or intolerance to excipients to amivantamab, cetuximab, bevacizumab, or FOLFIRI.
4. Participant has a history of clinically significant cardiovascular disease, including but not limited to the conditions specified in the 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.
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.
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).
7. Participant with known mismatch repair deficiency (dMMR)/ high microsatellite instability (MSI-H) status who has not received immunotherapy treatments.
8. Participant with known Receptor tyrosine-protein kinase erbB-2 (HER2) -positive/amplified tumour.
9. Has prior exposure to irinotecan, or any agents that target epidermal growth factor (EGFR) or mesenchymal epithelial transition (MET), or both.
10. Participant with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
11. Known to be homozygous (has two identical alleles [versions]) for the genes UGT1A1*28 or *6 alleles or is compound or double heterozygous for the UGT1A1*28 and *6 alleles per local guidelines.
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 protocol specified criteria.
15. Has active hepatitis of infectious origin at screening.
16. Has had prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anticancer agent within 2 weeks or 4 half-lives whichever is longer, before the first administration of study intervention(s). For agents with long half-lives, the maximum required time since last dose is 4 weeks. The maximum required time since last dose is 28 days.
17. Had radiation therapy within 28 days before randomisation.
18. Has toxicities from previous anticancer therapies not resolved to baseline levels or to Grade less than or equal to 1 prior to randomisation (except for alopecia or post-radiation skin changes [any grade], Grade less than or equal to 2 peripheral neuropathy, and Grade less than or equal to 2 hypothyroidism stable on hormone replacement).
19. Requires a prohibited medication that cannot be discontinued, substituted, or temporarily interrupted during the study.
20. Received an investigational treatment (including investigational vaccines but not including anticancer therapy) or used an invasive investigational medical device within 8 weeks of randomisation.
21. 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
26/11/2024

Date of final enrolment
13/10/2026

Locations

Countries of recruitment
United Kingdom

England

Australia

Belgium

Brazil

China

France

Germany

Hungary

India

Israel

Italy

Japan

Malaysia

Mexico

Netherlands

Poland

Romania

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