# OrigAMI-2: A randomized, phase 3 study of amivantamab vs cetuximab, both in combination with FOLFOX or FOLFIRI, as first-line treatment in left-sided *RAS/BRAF* wild-type metastatic colorectal cancer

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## Summary

OrigAMI-2 is a randomized, open-label, phase 3 study evaluating the efficacy of amivantamab SC compared with cetuximab IV, both in combination with chemotherapy, as 1L therapy in participants with L-sided unresectable or metastatic CRC that is WT for *KRAS*, *NRAS*, and *BRAF* by local testing, and who have not previously received treatment for advanced disease

## Current status

OrigAMI-2 is currently enrolling, with a goal of 1000 participants

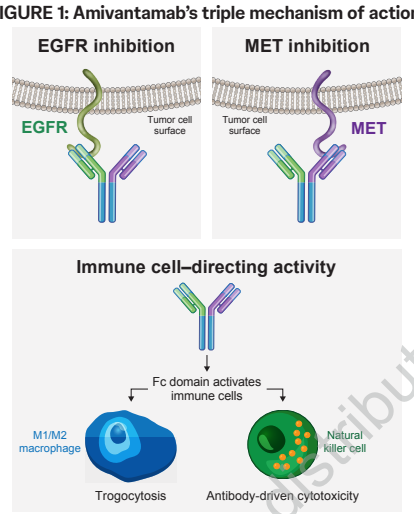
## Registration information

This study is registered with ClinicalTrials.gov (Identifier: NCT06662786)

## Background

- Approximately 50% of patients with metastatic colorectal cancer (CRC) have tumors that are wild-type (WT) for *KRAS*, *NRAS*, and *BRAF* (*RAS*/*BRAF* WT)[1]
- Standard first-line (1L) therapy for left-sided (L-sided) metastatic CRC is doublet chemotherapy (FOLFOX or FOLFIRI) combined with an anti–epidermal growth factor receptor (EGFR) therapy,[2] but resistance is nearly inevitable[3,4]
  - Clinical outcomes for metastatic CRC are poor, with 5-year survival rates in the United States of <20%[5]
  - In 1L RAS WT metastatic CRC, cetuximab plus FOLFIRI demonstrated a median progression-free survival of 11.4 months and a median overall survival of 28.4 months[6]
- *MET* alterations are known resistance mechanisms to EGFR inhibition[4,7,8]
- Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity (**Figure 1**),[9] is US Food and Drug Administration approved for multiple indications in *EGFR*-mutated advanced non-small cell lung cancer[10]
- In the phase 1b/2 OrigAMI-1 study (ClinicalTrials.gov Identifier: NCT05379595), amivantamab plus FOLFOX or FOLFIRI demonstrated rapid and durable antitumor activity, regardless of tumor sidedness, in participants with *RAS*/*BRAF* WT metastatic CRC[11]
  - Objective response rate was 64% (7/11 participants [complete response, 1; partial response, 6; stable disease, 3; progressive disease, 1]) among participants with L-sided *RAS*/*BRAF* WT metastatic CRC who received 1L amivantamab plus FOLFOX or FOLFIRI[11]

**FIGURE 1: Amivantamab's triple mechanism of action**




EGFR, epidermal growth factor receptor.

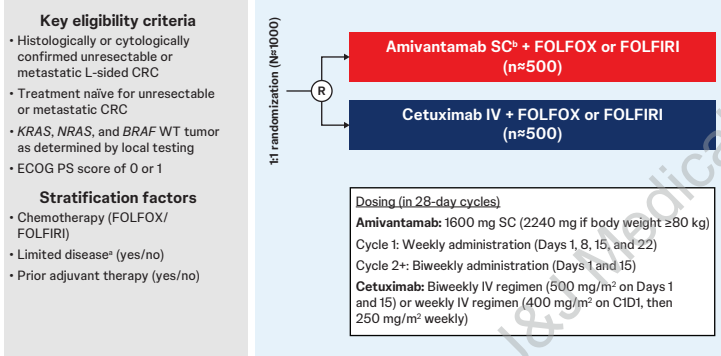
## Objective

- The phase 3, randomized OrigAMI-2 study will evaluate the efficacy and safety of subcutaneous (SC) amivantamab (co-formulated with recombinant human hyaluronidase PH20) compared with intravenous (IV) cetuximab, both in combination with FOLFOX or FOLFIRI, as 1L therapy for participants with L-sided *RAS*/*BRAF* WT unresectable or metastatic CRC

## Methods

- OrigAMI-2 is a randomized, open-label, phase 3 study (ClinicalTrials.gov Identifier: NCT06662786) currently recruiting participants with L-sided unresectable or metastatic CRC (**Figure 2**)
  - L-sided CRC is defined as a primary tumor arising from the splenic flexure, descending colon, sigmoid colon, rectosigmoid, or rectum that has been histologically or cytologically confirmed
- Participants will be randomized 1:1 to receive amivantamab SC or cetuximab IV, both in combination with chemotherapy (FOLFOX or FOLFIRI per investigator's discretion)
- Participants may undergo curative-intent surgery/procedure if appropriate during the treatment period
  - All cases will be reviewed by an independent committee prior to the intervention

**FIGURE 2: OrigAMI-2 study design**




[a]Defined as ≤2 metastatic sites and ≤5 metastatic lesions in each site. [b]Co-formulated with 2000 U/mL rHuPH20. [c]For participants who undergo curative-intent surgery/procedure during the treatment period, preintervention imaging will be used to determine the best response of CR, PR, or SD, and postintervention tumor assessments will be used to determine the time and location of PD (eg, recurrence at the site of resection or a distant new lesion).
AE, adverse event; BICR, blinded independent central review; C, Cycle; CR, complete response; CRC, colorectal cancer; D, Day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; IV, intravenous; L-sided, left-sided; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events v5.0; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; RECIST v1.1, Response Evaluation Criteria in Solid Tumors v1.1; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SD, stable disease; TTF, time to treatment failure; WT, wild-type.

- Key inclusion and exclusion criteria are shown in **Table 1**

**TABLE 1: Key inclusion and exclusion criteria**

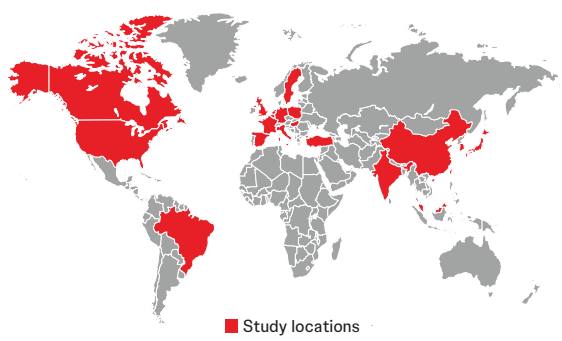
| Inclusion criteria | Exclusion criteria |
|---|---|
| • ≥18 years of age<br>• Histologically or cytologically confirmed unresectable or metastatic L-sided CRC<br>• *KRAS*, *NRAS*, and *BRAF* WT tumor as determined by local testing<br>• Consent to the submission of fresh tumor tissue<br>• Treatment naïve for unresectable or metastatic CRC<br>– Prior adjuvant[a] or neoadjuvant[b] therapy in nonmetastatic disease is permitted but must have concluded >12 months prior to CRC recurrence/metastases<br>• ECOG PS score of 0 or 1<br>• May have brain metastases if definitively and locally treated, clinically stable, and asymptomatic for ≥2 weeks | • History of or current ILD, pneumonitis, or pulmonary fibrosis<br>• Known allergies, hypersensitivity, or intolerance to any component of the study treatment<br>• Known dMMR/MSI-H status and HER2-positive/-amplified tumor<br>• Prior exposure to agents that target EGFR or MET<br>• History or known presence of leptomeningeal disease or spinal cord compression<br>• Active hepatitis of infectious origin |

[a]Adjuvant chemotherapy that included fluoropyrimidine alone or in combination with oxaliplatin or irinotecan (≤6 months of treatment) or radiation with radiosensitizing chemotherapy.
[b]Neoadjuvant chemotherapy with fluoropyrimidine monotherapy.
CRC, colorectal cancer; dMMR, mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; L-sided, left-sided; MSI-H, microsatellite instability–high; WT, wild-type.

## OrigAMI-2 enrollment sites

- The multicenter, global OrigAMI-2 study is planned to open at ~216 sites in 22 locations (**Figure 3**)

**FIGURE 3: OrigAMI-2 enrollment sites**

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## Disclosures

**DA** served as an invited speaker for Amgen, Aptitude Health, art tempi communications, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Clinical Care Options, Eisai, From Research to Practice, GSK, iMedX, IOMEDICO (Germany), Ipsen, MCI, Merck Serono, Merck Sharp & Dohme, Peer MD (China), PRMA Consulting, Sanofi (Genzyme), Seagen, Servier, Sirtex, STEAMitUP Germany, Tactics MD LLC, Takeda, Terumo, Viatris, and WebMD Health Corp; participated in an advisory board for Amgen, AstraZeneca, Boston Scientific, Bristol Myers Squibb, CRA International, Gilead, Janssen Cilag, Merck Sharp & Dohme, Onkowissen, Pierre Fabre Pharma, Seagen, Takeda, and Terumo; received funding from AbbVie; served as an associate editor of *Clinical Colorectal Cancer*, *ESMO Open*, and *Annals of Oncology*; served as the coordinating primary investigator for OncoLytics; served in advisory or leadership roles for OncoLytics, Phanes Therapeutics Inc, AIO (German Cancer Society), and EORTC; and received other financial interests from Sanofi (Genzyme). **AC** served in a consulting or advisory role for Amgen, Foundation Medicine, Merck Serono, Roche, and Transgene; 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