ORIGAMI-1

Antitumor activity of amivantamab by consensus molecular subtypes in *RAS/BRAF* wild-type metastatic colorectal cancer: Secondary analyses from the phase 1b/2 OrigAMI-1 study

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Key Takeaway

In a refractory 3L+ population, amivantamab monotherapy, with its dual targeting of EGFR and MET, demonstrated consistent antitumor activity in both canonical *EGFR*-dependent (CMS2) and mesenchymal *EGFR*-independent (CMS4) mCRC tumors

Conclusions

- Majority of biopsied *RAS/BRAF* WT mCRC tumors in this refractory setting were CMS2 (canonical *EGFR*) or CMS4 (mesenchymal)
- Unlike traditional EGFR inhibitors, PFS (4.2 vs 5.3 months) and OS (11.3 vs 13.5 months) were similar in CMS2 versus CMS4, respectively, among participants treated with amivantamab in this refractory *RAS/BRAF* WT setting
- Antitumor activity was observed with or without subtype switching; amivantamab led to decreases in *AREG* and *EREG* and an increase in *HGF* expression, independent of subtype or response

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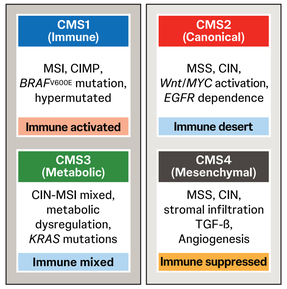
Introduction

- Colorectal tumors can be classified into 4 consensus molecular subtypes (CMS; **Figure 1**)[1, 2]
- In *RAS/BRAF* wild type (WT) metastatic colorectal cancer (mCRC), the majority of tumors are classified as canonical *EGFR*-dependent (CMS2) and mesenchymal *EGFR*-independent (CMS4), with the latter associated with poor prognosis and limited response to traditional EGFR inhibition[2, 3]
  - In prior analyses, cetuximab monotherapy demonstrated greater antitumor activity against CMS2 versus CMS4 tumors[4]
  - Additionally, CMS2 to CMS4 subtype switching has been described as a potential cetuximab monotherapy resistance mechanism[3]
- Amivantamab, an EGFR-MET bispecific antibody, has demonstrated antitumor activity in refractory mCRC, independent of sidedness[5]
- **Given the role of *HGF/MET* signaling in the mesenchymal subtype (CMS4),[3] targeting with amivantamab could demonstrate antitumor activity in both CMS2 and CMS4 mCRC**

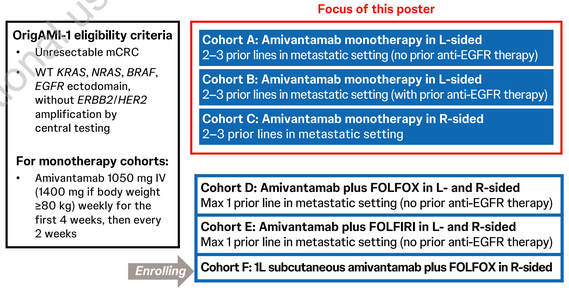
Figure 1: CMS in colorectal cancer[1]



Methods

- OrigAMI-1 (ClinicalTrials.gov Identifier: NCT05379595) is assessing amivantamab as monotherapy or combined with FOLFOX or FOLFIRI in *RAS/BRAF* WT mCRC (**Figure 2**)
- For Cohorts A, B, and C (third- or later-line population):
  - Exploratory analyses involving CMS groups were conducted
  - CMS assignment and expression changes in key EGFR/MET ligands at baseline (n=76) and Cycle 3 Day 1 (C3D1; n=17) were analyzed by whole-transcriptome RNA-sequencing of biopsies
- Data cutoff was October 31, 2024; primary results from the monotherapy cohorts were published in 2026 in *J Clin Oncol*[5]

Figure 2: OrigAMI-1 study design



Results

- Among biopsied samples at baseline, CMS2 (n=42) and CMS4 (n=31) comprised 96% (73/76) of tumors
- Baseline characteristics were generally similar between CMS2 and CMS4, except for a higher percentage of liver metastases in CMS2 (**Table 1**)

Table 1: Demographic and baseline disease characteristics

Characteristic, n (%)	CMS2 (n=42)	CMS4 (n=31)
Median (range) age, years	63.5 (40–80)	62.0 (35–78)
Male	30 (71)	19 (61)
Race		
Asian	29 (69)	18 (58)
White	11 (26)	11 (35)
Black or African American	1 (2)	1 (3)
Other[a]	1 (2)	1 (3)
ECOG PS score: 0 / 1	22 (52) / 20 (48)	14 (45) / 17 (55)
Tumor side: left / right	34 (81) / 8 (19)	22 (71) / 9 (29)
No. of prior lines[b]: 2 / 3	24 (57) / 18 (43)	18 (58) / 13 (42)
Prior bevacizumab	40 (95)	29 (94)
Prior anti-EGFR therapy[c]	25 (60)	22 (71)
Liver metastases	37 (88)	21 (68)

[a]Includes American Indian or Alaska Native and not reported. [b]In the metastatic setting. [c]Includes cetuximab and panitumumab.

Efficacy

- Clinical outcomes with amivantamab for CMS2 and CMS4 were consistent (**Table 2**)
  - Progression-free survival (PFS) and overall survival (OS) were not significantly different between the CMS2 and CMS4 subgroups (**Figure 3**; *P*=0.5 for PFS and *P*=0.6 for OS)

Table 2: Efficacy outcomes in refractory *RAS/RAF* WT mCRC

Endpoint	CMS2 (n=42)	CMS4 (n=31)
Objective response rate	26% (95% CI, 14–42)	16% (95% CI, 5–34)
Disease control rate[a]	83% (95% CI, 69–93)	74% (95% CI, 55–88)
PFS	4.2 months (95% CI, 3.6–5.6)	5.3 months (95% CI, 3.5–5.7)
OS	11.3 months (95% CI, 8.1–16.2)	13.5 months (95% CI, 8.1–NE)

NE, not estimable.
[a]Disease control rate is defined as the percentage of participants achieving a best overall response of CR, PR, or SD (with a minimum duration of 7 weeks).

Biomarkers

- At baseline (n=73):
  - Genomic profiles derived from ctDNA were similar
  - *AREG* and *EREG* mRNA expression was higher in CMS2
- Among participants with paired biopsies at baseline and C3D1 (n=17)
  - At C3D1, antitumor activity was seen in participants with subtype switching (2/5 responded) and without subtype switching (5/11 responded; **Figure 4**)
  - Amivantamab treatment generally decreased *AREG* and *EREG* expression and increased *HGF* expression, independent of subtype or response (**Figure 5**)

Figure 3: (A) PFS and (B) OS among CMS2/CMS4 subgroups following amivantamab treatment in refractory *RAS/RAF* WT mCRC

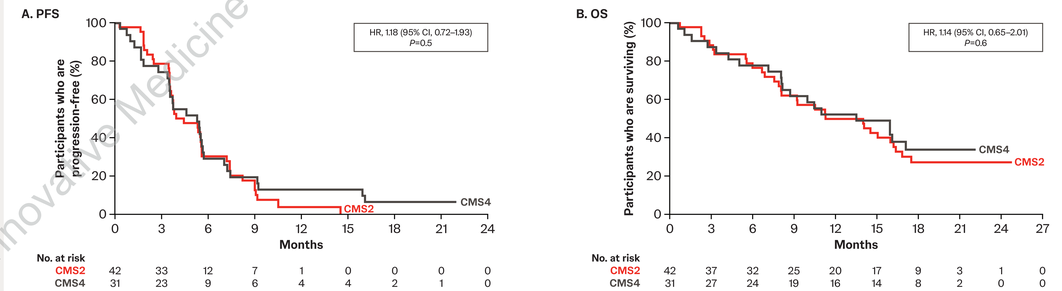
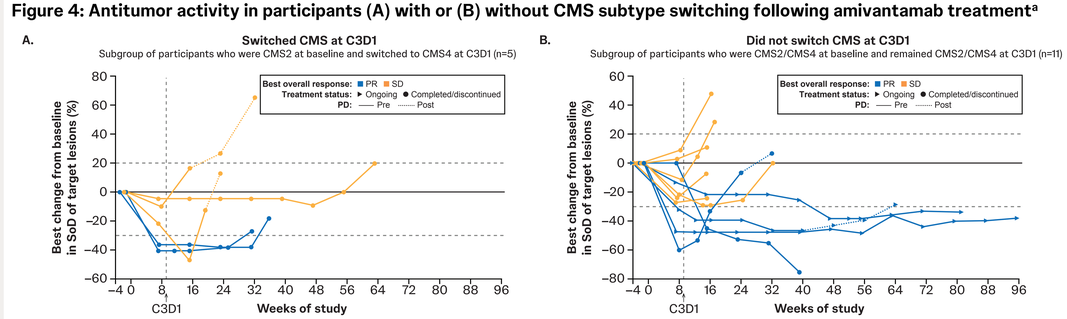
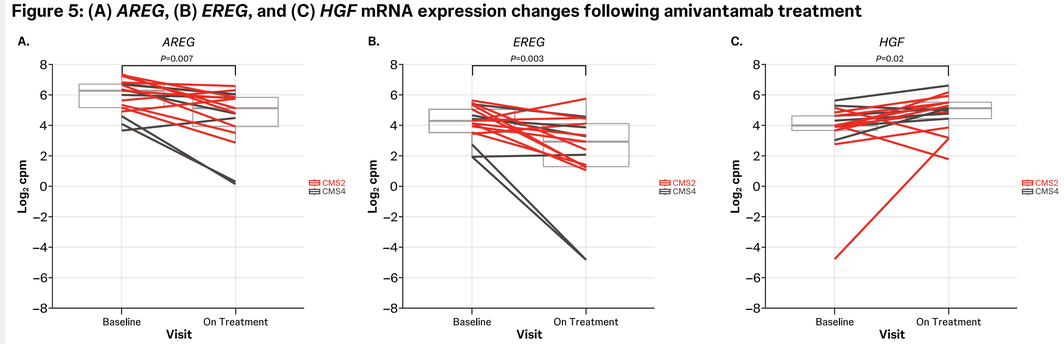


Figure 4: Antitumor activity in participants (A) with or (B) without CMS subtype switching following amivantamab treatment[a]



[a]One participant switched from CMS2 to CMS1 in C3D1 (not shown).

Figure 5: (A) *AREG*, (B) *EREG*, and (C) *HGF* mRNA expression changes following amivantamab treatment



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Solid Tumors

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