Amivantamab with and without chemotherapy in right-sided advanced or metastatic colorectal cancer: Updated results from OrigAMI-1, an open-label, phase 1b/2 study

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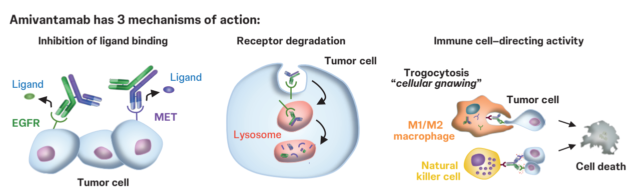
Background

- Anti-epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) with chemotherapy (FOLFOX or FOLFIRI) are frequently used to treat left-sided (L-sided) but not right-sided (R-sided) *RAS/BRAF* wild-type (WT) metastatic colorectal cancer (mCRC)[1]
- While mesenchymal-epithelial transition (MET) inhibitors are not currently used in routine mCRC therapy,[1] high MET expression is associated with poor prognosis in mCRC and, regardless of location, acquired *MET* alterations can lead to resistance to anti-EGFR therapies[2–4]
- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[5] that is approved by the US Food and Drug Administration in 4 *EGFR*-mutant advanced non-small cell lung cancer indications[6] (**Figure 1**)
- Amivantamab has shown promising antitumor activity in *RAS/BRAF* WT mCRC[7]
- Here, we present updated activity data on amivantamab as a monotherapy and in combination with FOLFOX/FOLFIRI in R-sided *RAS/BRAF* WT mCRC,[7] where there is an unmet need for more effective therapies

FIGURE 1: Amivantamab's mechanisms of action

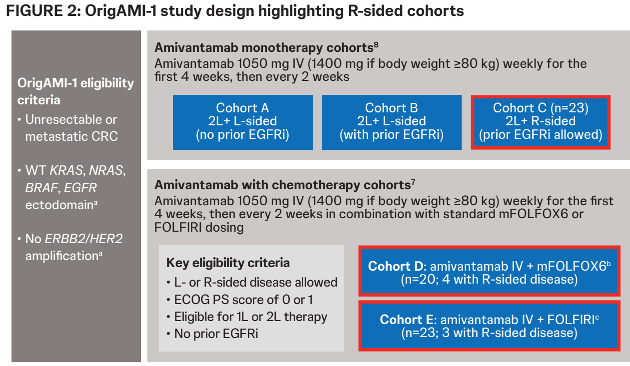


EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition.

Methods

- OrigAMI-1 (ClinicalTrials.gov Identifier: NCT05379595) is a global, multicenter, open-label, phase 1b/2 study of amivantamab monotherapy with or without standard-of-care chemotherapy in patients with advanced or metastatic CRC (**Figure 2**)
- The analyses here assessed the efficacy and safety of
  – Amivantamab intravenous (IV) as a monotherapy in patients with R-sided disease who had 2 or 3 prior lines of therapy (**prior EGFR inhibitor therapy allowed; Cohort C, prespecified analyses**)
  – Amivantamab IV in combination with chemotherapy (mFOLFOX6 or FOLFIRI) in patients with R-sided disease who had a maximum of 1 prior line of therapy and **no prior EGFR inhibitor therapy (Cohorts D and E, post hoc analyses)**
- R-sided disease was defined as a primary tumor arising from the cecum, ascending colon, or transverse colon
- The association between biomarkers and clinical response was also assessed in an exploratory analysis

FIGURE 2: OrigAMI-1 study design highlighting R-sided cohorts



OrigAMI-1 (ClinicalTrials.gov Identifier: NCT05379595); clinical cutoff: October 31, 2024.
[a]Central ctDNA testing was performed at screening to identify *KRAS/NRAS* missense alterations (leading to G12X, G13X, Q61X, K117X, A59X, or A146X), *BRAF* missense alterations (leading to V600X change), or *ERRB2/HER2* amplification, as detected by Guardant360 CDx. [b]mFOLFOX6 comprises oxaliplatin (85 mg/m²) IV, leucovorin 400 mg/m² (or 200 mg/m² if levoleucovorin) IV, 5-FU bolus (400 mg/m²) IV, and 5-FU (2400 mg/m² or 1200 mg/m²/day for 2 days). [c]FOLFIRI comprises irinotecan (180 mg/m²) IV, leucovorin 400 mg/m² (or 200 mg/m² if levoleucovorin) IV, 5-FU bolus (400 mg/m²) IV, and 5-FU (2400 mg/m² or 1200 mg/m²/day for 2 days).
1L, first-line; 2L, second-line; 5-FU, 5-fluorouracil; CRC, colorectal cancer; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRi, epidermal growth factor receptor inhibitor; IV, intravenous; L-sided, left-sided; R-sided, right-sided; WT, wild-type.

Results

Baseline demographic and clinical characteristics

- A total of 30 patients were included in this analysis (**Table 1**)
- Patients in OrigAMI-1 were heavily pretreated, with up to 3 prior lines of therapy in the amivantamab monotherapy cohort

TABLE 1: Baseline demographic and clinical characteristics

Characteristic	Amivantamab monotherapy (n=23)	Amivantamab + FOLFOX or FOLFIRI (n=7)
Age, median (range), years	60 (34–79)	61 (36–74)
Male, n (%)	13 (57)	6 (86)
Race, n (%)		
Asian	13 (57)	5 (71)
Black or African American	1 (4)	1 (14)
White	6 (26)	1 (14)
Other[a]	3 (13)	0
ECOG PS score, n (%)		
0	9 (39)	2 (29)
1	14 (61)	5 (71)
Median number of prior lines of therapy in the metastatic setting, n (range)	2 (1–3)	1 (1–1)
Prior EGFRi, n (%)	10 (43)	0
Liver metastases,[b] n (%)	18 (78)	6 (86)
Primary tumor location, n (%)		
Cecum	0	1 (14)
Ascending colon	9 (39)	4 (57)
Hepatic flexure	7 (30)	1 (14)
Transverse colon	7 (30)	1 (14)

[a]Includes patients who identified as American Indian or Alaska Native, patients who identified as multiple races, and patients who did not report a race. [b]Patients could have metastases at more than 1 location. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRi, epidermal growth factor receptor inhibitor.

Safety

- No discontinuations related to amivantamab were reported in any cohort among patients with R-sided disease in OrigAMI-1 (**Table 2**)

TABLE 2: Safety

TEAEs (≥20%) by preferred term, n (%)	Amivantamab monotherapy (n=23)		Amivantamab + FOLFOX or FOLFIRI (n=7)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Dermatitis acneiform	7 (30)	1 (4)	2 (29)	0
Diarrhea[a]	6 (26)	0	5 (71)	1 (14)
Rash	6 (26)	1 (4)	4 (57)	1 (14)
Stomatitis	6 (26)	0	6 (86)	0
Pruritus	5 (22)	0	1 (14)	0
Paronychia	4 (17)	0	3 (43)	0
Associated with MET inhibition				
Hypoalbuminemia	8 (35)	3 (13)	1 (14)	0
Peripheral edema	6 (26)	0	0	0
Other				
IRR	14 (61)	0	4 (57)	0
Fatigue	7 (30)	0	2 (29)	0
Nausea	6 (26)	0	3 (43)	0
Constipation	6 (26)	0	2 (29)	0
ALT increased	5 (22)	1 (4)	1 (14)	0
Anemia	5 (22)	1 (4)	1 (14)	0
AST increased	5 (22)	1 (4)	1 (14)	0
Insomnia	5 (22)	0	1 (14)	0
Vomiting	5 (22)	0	1 (14)	0
Ascites	5 (22)	2 (9)	0	0
Hypokalemia	3 (13)	2 (9)	2 (29)	1 (14)
Weight decreased	2 (9)	0	3 (43)	0
Asthenia	2 (9)	0	2 (29)	0
Thrombocytopenia	1 (4)	0	4 (57)	1 (14)
Neutropenia	0	0	5 (71)	3 (43)
Leukopenia	0	0	3 (43)	0
Dry mouth	0	0	2 (29)	0
Flatulence	0	0	2 (29)	0

[a]Also associated with 5FU, a component of the FOLFOX regimen, and with irinotecan, a component of the FOLFIRI regimen.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; MET, mesenchymal-epithelial transition; TEAE, treatment-emergent adverse event.

Efficacy

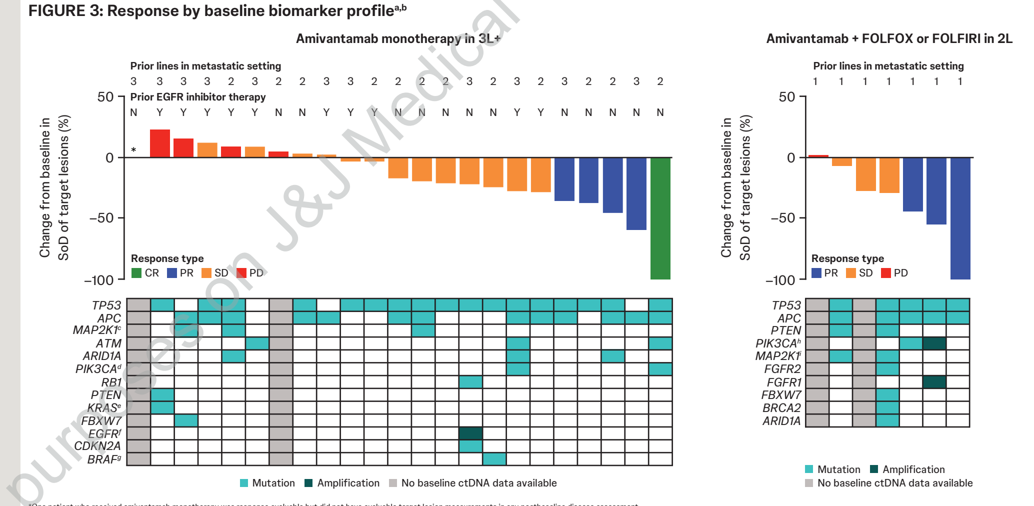
- Objective response rate (ORR), median duration of response (mDoR), disease control rate (DCR), and median progression-free survival (mPFS) are shown in **Table 3**
- There is evidence of activity across a range of mutations, including those conferring resistance to anti-EGFR therapy (**Figure 3**)
- Median (range) follow-up was 8.1 months (0.6–20.3) for the 23 patients receiving amivantamab monotherapy and 8.2 months (3.2–11.9) for the 7 patients receiving amivantamab + chemotherapy (**Figure 4**)

TABLE 3: Efficacy endpoints

Endpoint	Amivantamab monotherapy in 3L+ (n=23)	Amivantamab + FOLFOX or FOLFIRI in 2L (n=7)
ORR,[a] % (95% CI) (No. of patients)	22 (8–44) (n=5)	43 (10–82) (n=3)
Median DoR,[b] mo (95% CI)	9.8 (3.7–NE)[c]	NE (5.8–NE)[d]
DCR, % (95% CI) (No. of patients)	78 (56–93) (n=18)	86 (42–100) (n=6)
Median PFS, mo (95% CI)	3.7 (3.4–5.5)	7.4 (1.8–NE)

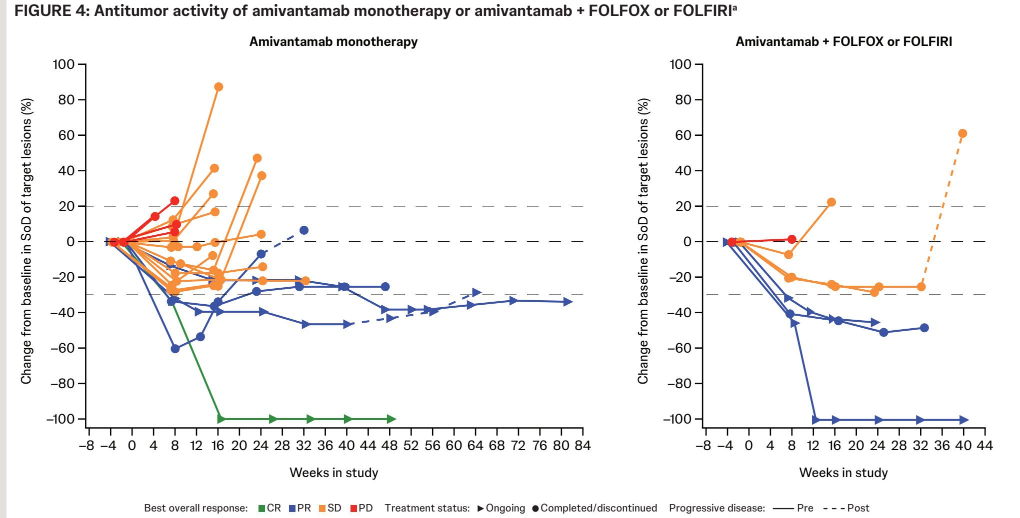
[a]ORR is the proportion of patients achieving PR or CR by investigator assessment at ≥2 consecutive disease assessments. [b]Among confirmed responders. [c]Of the 5 responders, 3 remain on treatment and have ongoing response. [d]All 3 responders remain on treatment; 1 of 3 responders has ongoing response.
2L, second-line; 3L+, third-line or higher; CI, confidence interval; CR, complete response; DCR, disease control rate (confirmed responders and patients with confirmed stable disease); DoR, duration of response; mCRC, metastatic colorectal cancer; mo, months; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

FIGURE 3: Response by baseline biomarker profile[a,b]



*One patient who received amivantamab monotherapy was response evaluable but did not have evaluable target lesion measurements in any postbaseline disease assessment.
[a]All variants are mutations unless otherwise stated. [b]No MET amplification was identified in this baseline assessment using ctDNA analyses. [c]Mutations included *MAP2K1* K57T and K57N. [d]Mutations included *PIK3CA* H1047R and R88Q. [e]Patient had a *KRAS* V14I mutation, which was not an exclusion criterion for the OrigAMI-1 study. [f]Patient had an *EGFR* amplification. [g]Patient had a *BRAF* D594G mutation, which was not an exclusion criterion for the OrigAMI-1 study. [h]Mutations included *PIK3CA* amplification and E542K. [i]Mutations included *MAP2K1* G128D and K57N.
CR, complete response; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

FIGURE 4: Antitumor activity of amivantamab monotherapy or amivantamab + FOLFOX or FOLFIRI[a]



[a]One patient in the amivantamab monotherapy cohort discontinued due to an adverse event prior to the first disease assessment and is not shown in the spider plot.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

Key takeaway

Amivantamab, an EGFR-MET bispecific antibody, as a monotherapy or combined with chemotherapy demonstrated durable antitumor activity in patients with R-sided *RAS/BRAF* WT mCRC, with a safety profile consistent with prior reports

Conclusions

- Amivantamab as a monotherapy or in combination with chemotherapy (FOLFOX or FOLFIRI) provided promising antitumor activity in patients with heavily pretreated R-sided *RAS/BRAF* WT mCRC
  – Amivantamab monotherapy in 3L+: ORR, 22%; DCR, 78%; mDoR, 9.8 months
    ▪ One patient achieved a complete response; 3 patients have ongoing response
  – Amivantamab + chemotherapy in 2L: ORR, 43%; DCR, 86%; mDoR, not estimable
    ▪ One patient has ongoing response
- The safety profile of amivantamab among patients with R-sided mCRC was consistent with prior reports
- Amivantamab showed activity in the R-sided setting across a range of mutations, including those conferring resistance to anti-EGFR therapy
- Other phase 3 studies are evaluating amivantamab in mCRC
  – Amivantamab versus cetuximab (both plus FOLFOX or FOLFIRI) as 1L treatment OrigAMI-2 (NCT06662786)
  – Amivantamab versus cetuximab or bevacizumab (all plus FOLFIRI) as 2L treatment in OrigAMI-3 (NCT06750094)

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References:

1. Cervantes A, et al. *Ann Oncol.* 2023;34(1):10–32. 2. Raghav K, et al. *Oncotarget.* 2016;7(34):54627–54631. 3. Kishiki T, et al. *Cancer Chemother Pharmacol.* 2014;73(4):749–757. 4. Parizadeh SM, et al. *IUBMB Life.* 2019;71(7):802–811. 5. Moores SL, et al. *Cancer Res.* 2016;76(13):3942–3953. 6. RYBREVANT® (amivantamab-vmjw) injection for intravenous use [package insert]. Janssen Biotech, Inc.; 2024. 7. Pietrantonio F, et al. *Ann Oncol.* 2024;35(suppl 2):S434. 8. Oberstein PE, et al. *J Clin Oncol.* 2024;42(3 suppl):135.