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ORIGAMI-1
Ami + FOLFOX or FOLFIRI in *RAS*/*BRAF* WT mCRC

Amivantamab plus FOLFOX or FOLFIRI in metastatic colorectal cancer

Results from OrigAMI-1, a phase 1b/2 study

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Declaration of Interests

Filippo Pietrantonio

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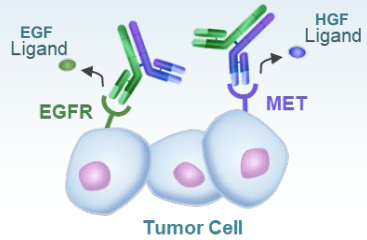
Background

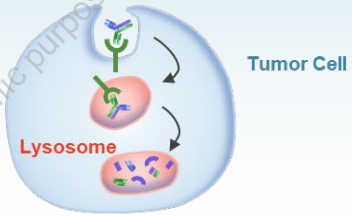
- EGFR inhibitors (panitumumab or cetuximab) in combination with chemotherapy are associated with an ORR of 32% to 36% in 2L *RAS*/*BRAF* WT mCRC[1,2]
- *MET* alterations are associated with metastatic progression and poor prognosis in patients with CRC, and are a common mechanism of resistance to EGFR inhibitors[3-6]
- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[7] that has shown promising monotherapy anti-tumor activity in right- and left-sided relapsed/refractory mCRC[8]

Amivantamab has 3 mechanisms of action:

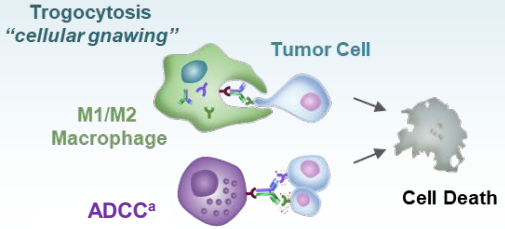
Inhibition of Ligand Binding



Receptor Degradation



Immune Cell-directing Activity



With its unique multi-targeted MOA, amivantamab plus FOLFOX or FOLFIRI may offer improved efficacy in *EGFR* inhibitor–naïve *RAS*/*BRAF* WT mCRC

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[a]ADCC involves release of perforins and granzymes to effect tumor cell death. ADCC, antibody-dependent cellular cytotoxicity; HGF, hepatocyte growth factor; ORR, objective response rate.

1. Iwamoto S, et al. *Anticancer Res*. 2014;34(4):1967-1974. 2. Peeters M, et al. *Ann Oncol*. 2014;25(1):107-116. 3. Raghav K, et al. *Oncotarget*. 2016;7(34):54627-54631. 4. Bardelli A, et al. *Cancer Discovery*. 2013;3(6):658-673. 5. Zeng ZS, et al. *Cancer Lett*. 2008;265(2):258-269. 6. Morano F, et al. *J Clin Oncol*. 2019;37(33):3099-3110. 7. Moores SL, et al. *Cancer Res*. 2016;76(13):3942-3953. 8. Oberstein PE, et al. *J Clin Oncol*. 2024;42(3 suppl):135.

OrigAMI-1: Phase 1b/2 Study Design

ORIGAMI-1
Ami + FOLFOX or FOLFIRI in *RAS*/*BRAF* WT mCRC

OrigAMI-1 Eligibility Criteria

- Unresectable or metastatic CRC
- Wild-type *KRAS*, *NRAS*, *BRAF*[a]
- No *ERBB2*/*HER2* amplification[a]

Amivantamab Monotherapy Cohorts (previously presented at ASCO-GI 2024)[1]

- Cohort A: 2L+ L-sided (no prior EGFRi)
- Cohort B: 2L+ L-sided (with prior EGFRi)
- Cohort C: 2L+ R-sided (prior EGFRi allowed)

Combination Cohorts ← Focus of this presentation

Dose escalation identified amivantamab 1050 mg IV (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks in combination with standard mFOLFOX6 or FOLFIRI dosing as the RP2D

Key Eligibility Criteria

- ECOG PS score of 0–1
- Eligible for 1L or 2L therapy
- No prior EGFRi

Cohort D: Amivantamab + mFOLFOX6 (n=20)

Cohort E: Amivantamab + FOLFIRI (n=23)

Primary Endpoint: Safety

Secondary Endpoints

- ORR
- DoR
- DCR
- PFS

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OrigAMI-1 (ClinicalTrials.gov Identifier: NCT05379595); clinical cut-off: 22-July- 2024.

[a]Central ctDNA testing was performed at screening to identify *KRAS* missense alterations, *NRAS* mutations, *BRAF* mutations (leading to V600X change), or *ERRB2*/*HER2* amplification. ctDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; EGFRi, epidermal growth factor receptor inhibitor; ORR, objective response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose.

1. Oberstein PE, et al. *J Clin Oncol.* 2024;42(3 suppl):135.

Baseline Characteristics

Characteristic	Amivantamab + FOLFOX (n=20)	Amivantamab + FOLFIRI (n=23)	Total (N=43)
Age, median (range), years	64.0 (39–79)	61.0 (36–69)	62.0 (36–79)
Male, n (%)	14 (70)	17 (74)	31 (72)
Race, n (%)			
Asian	10 (50)	15 (65)	25 (58)
Black or African American	1 (5)	1 (4)	2 (5)
White	9 (45)	7 (30)	16 (37)
ECOG PS score, n (%)			
0	11 (55)	11 (48)	22 (51)
1	9 (45)	12 (52)	21 (49)
Tumor side, n (%)			
Left-sided	15 (75)	20 (87)	35 (81)
Right-sided	5 (25)	3 (13)	8 (19)
No. of prior lines of therapy in the metastatic setting, n (%)			
0	8 (40)	3 (13)	11 (26)
1	12 (60)	20 (87)	32 (74)
Liver metastases, n (%)	14 (70)	17 (74)	31 (72)[a]

[a]One patient had a nontarget liver lesion.

Safety

Median duration of treatment was 5.2 months for amivantamab + FOLFOX and 5.7 months for amivantamab + FOLFIRI

TEAEs (≥25%) by preferred term, n (%)	Amivantamab + FOLFOX (n=20)		Amivantamab + FOLFIRI (n=23)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Stomatitis	11 (55)	0	11 (48)	0
Diarrhea[a]	11 (55)	1 (5)	14 (61)	2 (9)
Rash	10 (50)	2 (10)	10 (43)	1 (4)
Dermatitis acneiform	3 (15)	0	8 (35)	1 (4)
Paronychia	7 (35)	0	10 (43)	0
Associated with MET inhibition				
Hypoalbuminemia	7 (35)	0	14 (61)	1 (4)
Associated with chemotherapy (FOLFOX or FOLFIRI)				
Neutropenia	10 (50)	7 (35)	14 (61)	11 (48)
Anemia	4 (20)	0	7 (30)	1 (4)
Thrombocytopenia	6 (30)	3 (15)	2 (9)	0

TEAEs (≥25%) by preferred term, n (%)	Amivantamab + FOLFOX (n=20)		Amivantamab + FOLFIRI (n=23)	
	All grades	Grade ≥3	All grades	Grade ≥3
Other				
Fatigue	10 (50)	0	7 (30)	2 (9)
IRR	9 (45)	0	9 (39)	0
Vomiting	8 (40)	1 (5)	7 (30)	0
Hypokalemia	7 (35)	1 (5)	7 (30)	2 (9)
ALT increased	3 (15)	0	7 (30)	0
Nausea	6 (30)	1 (5)	13 (57)	0
Hypoesthesia	6 (30)	0	1 (4)	0
Peripheral sensory neuropathy	6 (30)	0	1 (4)	0
Constipation	5 (25)	0	7 (30)	0
Asthenia	5 (25)	0	4 (17)	1 (4)

Treatment-related discontinuations of amivantamab were 10% for amivantamab + FOLFOX and 9% for amivantamab + FOLFIRI

[a]Also associated with irinotecan, a component of the FOLFIRI regimen.

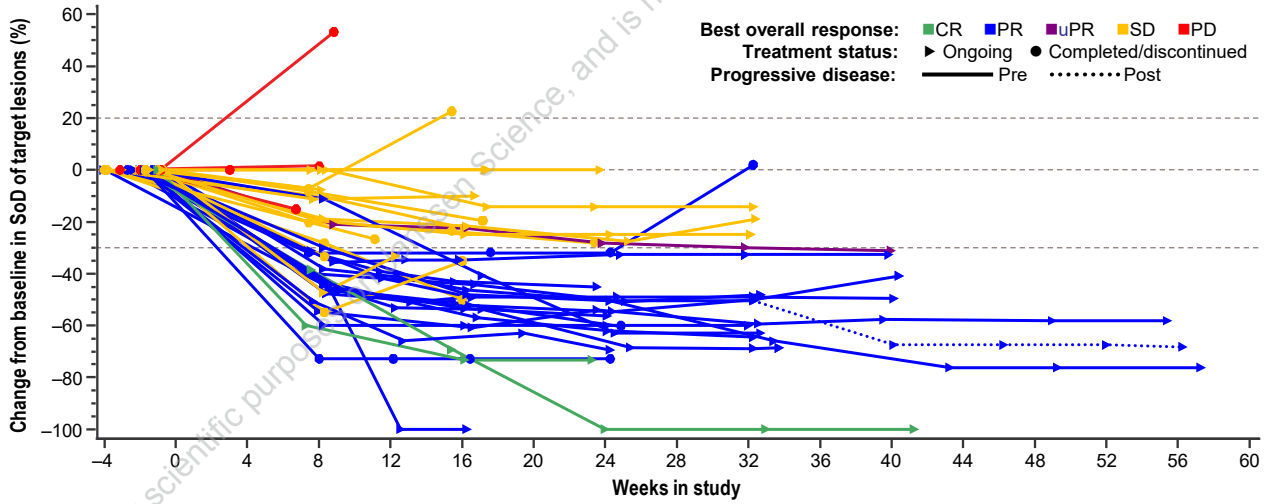
ALT, alanine aminotransferase; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Efficacy of Amivantamab + FOLFOX or FOLFIRI

Durable anti-tumor activity with amivantamab + FOLFOX or FOLFIRI

Investigator-assessed	Total (N=43)
ORR[a,b]	49% (95% CI, 33–65)
Median DoR[c]	7.4 months (95% CI, 5.6–NE)
Median time to response[c]	8.3 weeks
DCR	88% (95% CI, 75–96)
Median PFS	7.5 months (95% CI, 7.4–NE)
Received curative intent surgery, n	6 completed (3 more scheduled)

Patients could undergo curative intent surgery and were censored upon procedure completion



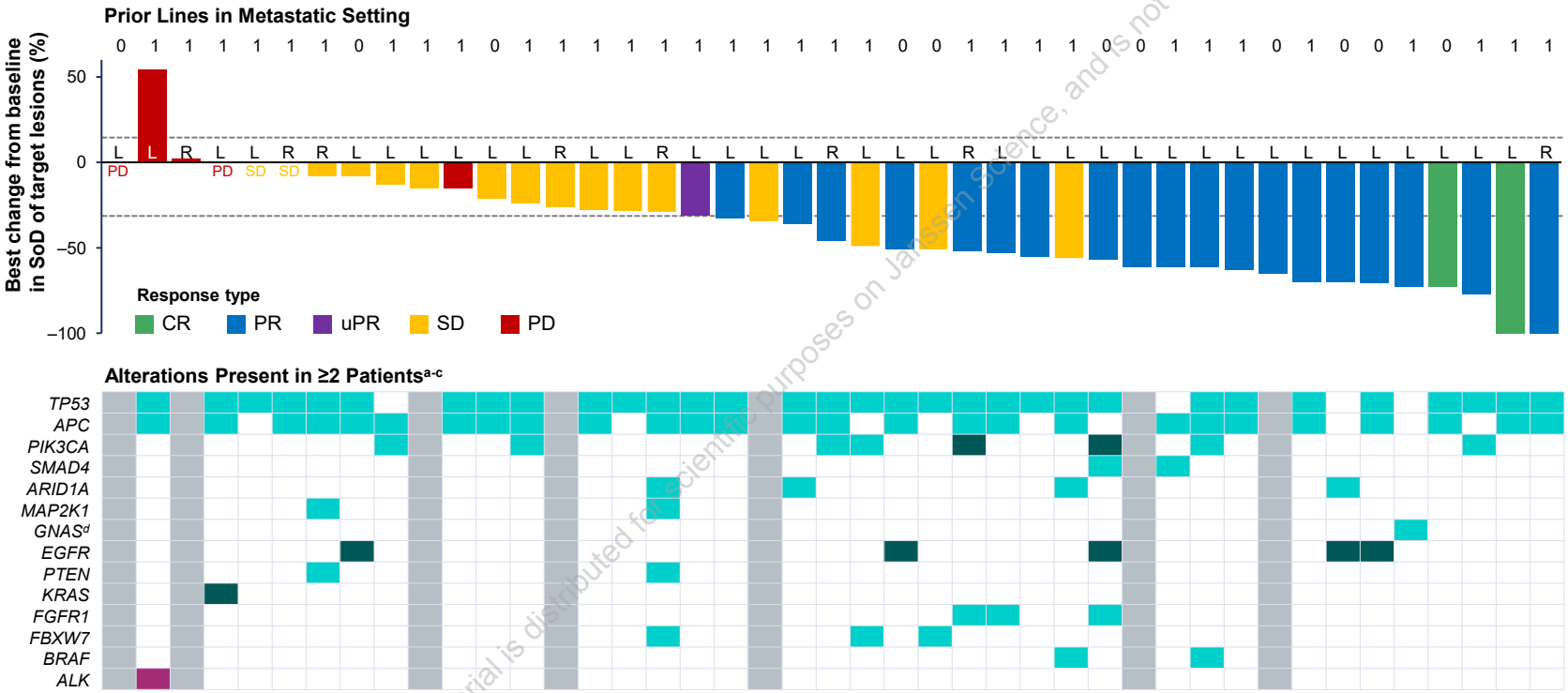
- Median (range) follow-up was 7.3 months (1.1–14.4)
- 67% (29/43) of patients remain on treatment[d]
- ORR was 64% among patients on 1L therapy and 44% among patients on 2L therapy

[a]ORR is the proportion of patients achieving PR or CR by investigator assessment at ≥2 consecutive disease assessments. [b]ORR among patients receiving amivantamab + FOLFOX was 60% (95% CI,36–81), and 39% (95% CI, 20–62) among patients receiving amivantamab + FOLFIRI. [c]Among confirmed responders. [d]One patient discontinued due to an adverse event prior to first disease assessment and is not shown in the spider plot.

1L, first-line; 2L, second-line; CR, complete response; DCR, disease control rate (confirmed responders and patients with confirmed stable disease); DoR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PFS, median progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameter; uPR, unconfirmed partial response.

Response by Biomarker Profile

Evidence of activity across a range of mutations, including those conferring resistance to anti-EGFR therapy



[a]All variants are mutations unless otherwise stated. [b]No *MET* amplification was identified in this baseline assessment using ctDNA analyses. [c]Mutations were detected in 1 patient each for *RB1, PTPN11, JAK2, FGFR2, BRCA1, BRCA2, ATM,* and *CDKN2A*; the patient with an *ALK* fusion had aggressive disease progression. [d]Present as a single mutation in 1 patient.

CR, complete response; ctDNA, circulating tumor DNA; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameter; uPR, unconfirmed partial response.

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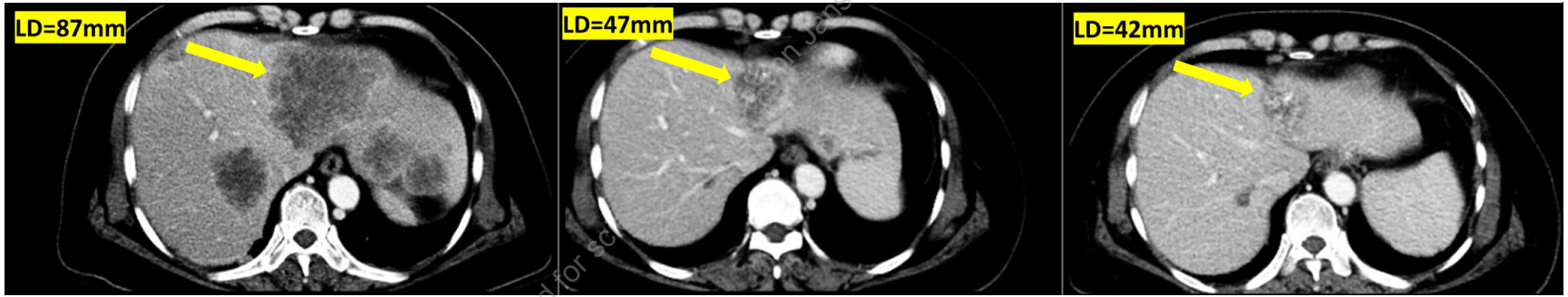
Intrahepatic Tumor Responses With Amivantamab + FOLFOX or FOLFIRI

The liver produces HGF, and amivantamab blocks HGF ligand binding to MET; therefore, we examined intrahepatic responses:

- 70% (30 of 43) of patients had measurable target liver lesions
- Intrahepatic outcomes: ORR, 53% (16 of 30); DCR, 93% (28 of 30)



- *65-year-old Asian female with no prior systemic treatment for colorectal cancer treated with amivantamab + FOLFIRI*
- *Partial hepatectomy, including segments 4/5/6/8, performed at 30 weeks*

Rapid tumor response and conversion to hepatectomy

DCR, disease control rate (includes confirmed responders and patients with confirmed stable disease); HGF, hepatocyte growth factor; ORR, objective response rate.

Conclusions

- Amivantamab + FOLFOX or FOLFIRI provided promising anti-tumor activity in patients with EGFR inhibitor–naïve 1L or 2L *RAS*/*BRAF* WT mCRC
  - ORR, 49%; DCR, 88%; mDoR, 7.4 months; mPFS, 7.5 months
- Clinically meaningful intrahepatic anti-tumor activity observed
  - Intrahepatic ORR, 53%; intrahepatic DCR, 93%
- 9 (21%) patients proceeded to curative intent surgery (6 completed, 3 scheduled) due to robust anti-tumor activity
- The safety profile of amivantamab + FOLFOX or FOLFIRI was consistent with each individual component, without additive toxicity
  - Low rates of treatment-related discontinuations

Amivantamab + FOLFOX or FOLFIRI showed rapid and durable anti-tumor activity, with curative potential and a manageable safety profile

1L, first-line; 2L, second-line; DCR, disease control rate (confirmed responders and patients with confirmed stable disease); mDoR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate.

Amivantamab + FOLFOX or FOLFIRI Advancing to Phase 3 Development in Colorectal Cancer

Phase 3 OrigAMI studies will use the more convenient subcutaneous formulation of amivantamab (~5-min manual push)

ORIGAMI-2

KRAS/NRAS and *BRAF* wild-type, **first-line,** left-sided, metastatic colorectal cancer

R 1:1

- **Amivantamab + FOLFOX or FOLFIRI (n~500)**
- **Cetuximab + FOLFOX or FOLFIRI (n~500)**

ORIGAMI-3

KRAS/NRAS and *BRAF* wild-type, EGFR inhibitor–naïve, recurrent or metastatic colorectal cancer post-chemo **(2L)**

R 1:1

- **Amivantamab + FOLFIRI (n~350)**
- **Cetuximab or bevacizumab + FOLFIRI (n~350)**

Also in Head and Neck

ORIGAMI-4

OrigAMI-4 (phase 1b/2): amivantamab alone or in addition to other treatment agents in recurrent or metastatic head and neck cancer (ClinicalTrials.gov Identifier: NCT06385080)

(OrigAMI-4 will also use the subcutaneous formulation of amivantamab.)

Acknowledgments

- Patients who participated in the study and their families and caregivers
- Physicians and nurses who cared for patients and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- Medical writing assistance was provided by Lumanity Communications Inc. and funded by Janssen Global Services, LLC

A total of 53 sites from 11 countries or territories are participating in the OrigAMI-1 study