Amivantamab treatment and intra-tumoral gene expression and immune cell changes in refractory metastatic colorectal cancer: Whole transcriptome RNA-sequencing analysis from the OrigAMI-1 study

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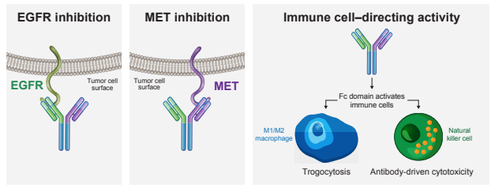
Background

- Anti–epidermal growth factor receptor (EGFR) antibodies (cetuximab and panitumumab) with chemotherapy (FOLFOX or FOLFIRI) can be used to treat left- and right-sided *RAS*/*BRAF* wild-type (WT) metastatic colorectal cancer (mCRC)[1]
- High *AREG* and *EREG* expression in mCRC has been shown to correlate with improved disease control and longer progression-free survival (PFS) with anti-EGFR therapy[2]
- High *MET* expression is associated with aggressive disease and a poor prognosis in mCRC, and acquired *MET* alterations can lead to resistance to anti-EGFR therapies[3-5]
- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity,[6] which is approved by the US Food and Drug Administration and the European Medicines Agency in several *EGFR*-mutated advanced non-small cell lung cancer indications[7,8] (**Figure 1**)
- Amivantamab monotherapy has shown promising activity in participants with refractory mCRC, independent of primary tumor sidedness (left or right)[9,10]
- Here, we analyzed gene expression data from the OrigAMI-1 study to identify mechanisms of sensitivity and action in response to amivantamab monotherapy

FIGURE 1: Amivantamab's triple mechanism of action



Methods

- The phase 1b/2 OrigAMI-1 study (ClinicalTrials.gov Identifier: NCT05379595) enrolled participants with mCRC harboring WT *KRAS*, *NRAS*, *BRAF* V600, and *EGFR* ectodomain, without *ERBB2*/*HER2* amplification (**Figure 2**)
- Participants with left-sided mCRC without prior anti-EGFR therapy (Cohort A) and with prior anti-EGFR therapy (Cohort B), as well as participants with right-sided mCRC with or without prior anti-EGFR therapy (Cohort C), received amivantamab intravenous (IV) monotherapy (1050 mg; 1400 mg if body weight ≥80 kg)
- Tumor biopsy samples were collected at screening and Cycle 3 Day 1 (C3D1; if feasible)
- Whole transcriptome RNA-sequencing data of paired baseline and C3D1 tumor samples were generated by Foundation Medicine
- Gene expression data were analyzed using standard bioinformatic methods to identify gene signatures associated with amivantamab treatment in baseline tumor samples (n=76) and paired baseline and C3D1 tumor samples (n=17)

FIGURE 2: OrigAMI-1 study design

Amivantamab phase 1b/2 dose expansion monotherapy cohorts

Amivantamab 1050 mg IV (1400 mg if body weight ≥80 kg) weekly for the first 4 weeks, then every 2 weeks

Key eligibility criteria
- Unresectable or metastatic CRC
- WT *KRAS*, *NRAS*, *BRAF* V600, *EGFR* ectodomain[a]
- No *ERBB2*/*HER2* amplification[a]
- Received 2 or 3 prior lines of systemic therapy in the metastatic setting

Cohort A: 3L+ left-sided, no prior EGFRi (n=16)

Cohort B: 3L+ left-sided, with prior EGFRi (n=43)

Cohort C: 3L+ right-sided, prior EGFRi allowed (n=17)

[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 *ERBB2*/*HER2* amplification, as detected by Guardant360® CDx.

Results

Efficacy by mRNA expression

- High baseline mRNA expression of *AREG* and *EREG* ligands was associated with treatment response across all cohorts (n=76; **Figure 3**)
- In Cohort A (n=16), median PFS was prolonged for participants with high (n=8) versus low (n=8) *AREG* expression, with medians of 9.1 versus 4.5 months, respectively (P<0.01)

Differential expression, *EGFR* pathway, and cell cycle pathway scores

- Differential expression analyses after amivantamab treatment showed significant changes in >800 genes (P<0.01) across all cohorts (n=17; **Figure 4A**)
- The *EGFR* pathway was significantly downregulated after amivantamab treatment (P<0.01; **Figure 4B**)
- Cell cycle pathway score was significantly downregulated following amivantamab treatment (P<0.01), implying reduced cell proliferation (**Figure 4C**)

Immune-related signature scores

- A significant upregulation of dendritic cell (P<0.005) and T cell–inflamed (P<0.05) signature scores was observed with amivantamab treatment across all cohorts (**Figure 5A-B**)
- Amivantamab also significantly increased the natural killer (NK) cell–mediated cytotoxicity pathway and cytolytic scores across all cohorts (both P<0.05; **Figure 5C-D**)

FIGURE 3: Baseline *EGFR* receptor and ligand mRNA expression tended to correlate with response

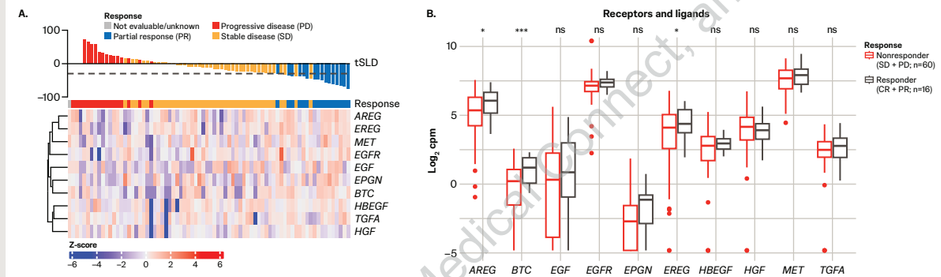
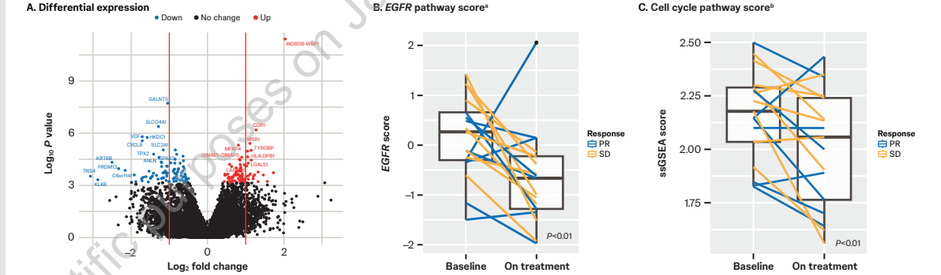
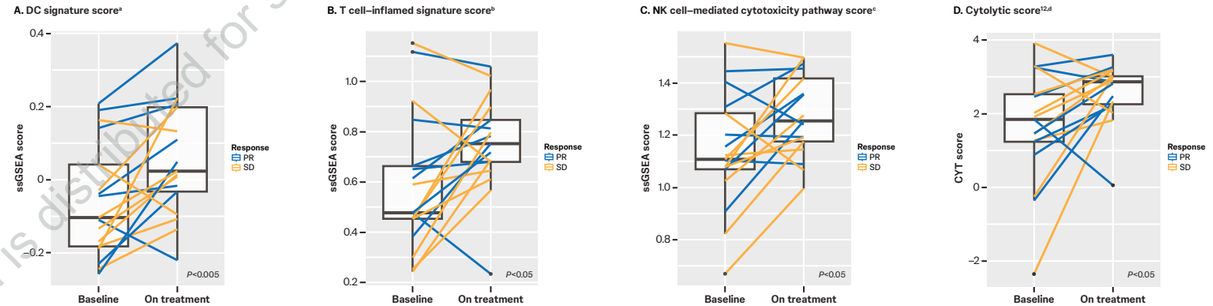


FIGURE 4: (A) Differential expression, (B) *EGFR* pathway score, and (C) cell cycle pathway score



Note: Significance of the score change was measured by paired Wilcoxon test.
[a]*EGFR* pathway scores were calculated using the PROGENy method.[11] [b]Gene list included in the cell cycle pathway was collected from the KEGG website. Pathway scores were calculated by the ssGSEA method.

FIGURE 5: Immune-related signature scores across cohorts



Note: Significance of the score change was measured by paired Wilcoxon test.
[a]DC gene signature obtained from the Biocarta and ssGSEA databases was used to calculate the signature score. [b]This 18-gene signature quantifies the T cell–inflamed microenvironment. [c]Gene list included in the cell cycle pathway was collected from the KEGG website. Pathway scores were calculated by the ssGSEA method. [d]Cytolytic score was defined as the mean of GZMA and PRF1.
DC, dendritic cell; NK, natural killer.

Key takeaways

ORIGAMI-1

Amivantamab increases cytotoxic immune cell signatures, which is consistent with immune cell infiltration into tumors, and downregulates the *EGFR* and cell cycle pathways

Elevated *AREG* and *EREG* ligand expression correlated with the response in WT mCRC

Conclusions

A significant upregulation of dendritic cell (P<0.005) and T cell–inflamed (P<0.05) signature scores was observed with amivantamab treatment, potentially implying increased immune cell infiltration of the tumor microenvironment

Amivantamab increased the cytolytic (P<0.05) and NK cell–mediated cytotoxicity pathway (P<0.05) scores, implying an increase in cytotoxic immune cells

AREG and *EREG* baseline mRNA levels were associated with response, and median PFS showed improvement for participants with high *AREG* expression in Cohort A (P<0.01)

Downregulation of cell cycle signatures was observed following amivantamab treatment, implying reduced tumor cell proliferation

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