

Clinical characteristics and outcomes by consensus molecular subtype in first-line anti-EGFR–treated RAS/RAF wildtype metastatic colorectal cancer

Elena Élez^{1,*}, Marcia Cruz-Correa², Parthiv J Mahadevia³, Sanjib Chowdhury⁴, Levon Demirdjian⁵, Filippo Pietrantonio⁶

¹Vall d'Hebron University Hospital, Barcelona, Spain; ²University of Puerto Rico, San Juan, Puerto Rico; ³Johnson & Johnson, Raritan, NJ, USA; ⁴Johnson & Johnson, Cambridge, MA, USA; ⁵Johnson & Johnson, San Diego, CA, USA; ⁶Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
*Presenting author: meelez@vhio.net

Key Takeaway

CMS4 and CMS2 tumors comprised 32% and 48% of cases, respectively, with CMS4 tumors showing worse survival outcomes versus CMS2 tumors in RAS/RAF WT MSS mCRC treated with 1L anti-EGFR therapy, highlighting the differential efficacy of anti-EGFR therapies for CMS4 versus CMS2 tumors

Conclusions

CMS classification was strongly prognostic in this real-world cohort of RAS/RAF WT MSS mCRC treated with 1L anti-EGFR therapy, with most patients having CMS4 (32%) and CMS2 (48%) tumors

CMS4 tumors were associated with less favorable clinical characteristics and poorer survival outcomes compared with CMS2, even after adjustment for baseline characteristics

Since CMS classification is not routinely performed at diagnosis, optimal 1L treatment strategies for RAS/BRAF WT mCRC should be effective across both subtypes to improve outcomes

CMS classification will be performed in the ongoing OrigAMI-2 and OrigAMI-3 trials to evaluate whether amivantamab, an EGFR-MET bispecific antibody, has an impact on the broader range of CMS subtypes versus cetuximab

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Introduction

- Consensus molecular subtypes (CMS) represent a biologically distinct classification of colorectal cancer (CRC) and have demonstrated prognostic relevance across multiple disease settings^{1,2}
- Among patients with RAS/RAF wildtype (WT) metastatic CRC (mCRC), anti-epidermal growth factor receptor (EGFR)–based therapy is a standard first-line (1L) treatment³
 - However, the relationship between CMS classification and outcomes in routine clinical practice remains incompletely characterized⁴
- Improved understanding of CMS-associated outcomes may help contextualize treatment performance across biologically distinct patient populations
- This study assessed CMS distribution and survival outcomes in patients with RAS/RAF WT microsatellite stable (MSS) mCRC treated with 1L anti-EGFR therapy

Results

- Patients with RAS/BRAF WT and MSS mCRC who received anti-EGFR therapy and chemotherapy in the 1L setting were included in the analysis (Figure 2)
- Demographic and clinical characteristics are shown in Table 1

Figure 2: Study population derivation

Flowchart illustrating the study population derivation:

- CRC and passed Tempus quality assurance (N=21,615)
- Metastatic CRC (n=17,534)
- Metastatic date between 2016 and 2022 (n=14,193)
- Tumor sample available that underwent RNA sequencing, had been treated with any first LoT after metastatic diagnosis, and received RNA sequencing testing at Tempus prior to or within 30 days of first LoT initiation (n=4,287)
- KRAS/NRAS/BRAF WT and MSS prior to or within 30 days of first LoT initiation (n=1,598)
- Received anti-EGFR therapy (cetuximab or panitumumab) and chemotherapy in first LoT* (n=238)

Final cohort breakdown by CMS:

- CMS1 (n=1)
- CMS2 (n=114)
- CMS3 (n=16)
- CMS4 (n=77)
- CMS UNK (n=30)

*Excludes 12 patients who received anti-EGFR therapy in the first LoT prior to receiving anti-vascular endothelial growth factor therapy in the first LoT.
CMS, consensus molecular subtype; LoT, line of therapy; MSS, microsatellite stable; UNK, unknown.

Table 1: Demographic and clinical characteristics

Characteristic, n (%)	CMS1 (n=1)	CMS2 (n=114)	CMS3 (n=16)	CMS4 (n=77)	CMS UNK (n=30)
Mean (SD) age, years	49.0 (NA)	55.6 (12.0)	62.8 (9.8)	56.7 (12.5)	54.6 (13.2)
Male	0	68 (60)	10 (63)	52 (68)	22 (73)
White	1 (100)	72 (63)	8 (50)	39 (51)	18 (60)
Stage at initial diagnosis (±60 days) ^a					
Stage III	0	18 (16)	1 (6)	22 (29)	3 (10)
Stage IV	1 (100)	79 (69)	15 (94)	43 (56)	22 (73)
Right-/left-sided ^b	0/	3 (3)/	0/	2 (3)/	2 (7)/
	1 (100)	65 (57)	13 (81)	49 (64)	18 (60)
Primary tumor site ^c					
Colon	1 (100)	74 (65)	8 (50)	46 (60)	16 (53)
Rectum	0	28 (25)	6 (38)	27 (35)	12 (40)
Metastatic site ^d					
Liver	1 (100)	83 (73)	8 (50)	27 (35)	20 (67)
Peritoneum	1 (100)	6 (5)	4 (25)	23 (30)	2 (7)
Lung	0	15 (13)	0	13 (17)	4 (13)
Other	0	9 (8)	1 (6)	22 (29)	4 (13)
Qualifying biopsy tissue site					
Colorectal	1 (100)	54 (47)	16 (100)	39 (51)	12 (40)
Liver	0	45 (39)	0	6 (8)	14 (47)
Non-liver	0	15 (13)	0	32 (42)	4 (13)
Chemotherapy backbone ^e					
FOLFOX	1 (100)	62 (54)	14 (88)	39 (51)	16 (53)
FOLFIRI	0	26 (23)	0	27 (35)	8 (27)
Anti-EGFR therapy					
Cetuximab	1 (100)	53 (46)	8 (50)	33 (43)	10 (33)
Panitumumab	0	61 (54)	8 (50)	44 (57)	20 (67)

^aOverall, 1% of patients had stage I disease and 4% had stage II disease; 9% had undocumented/UNK stages. ^bTwo patients had transverse tumors in the CMS3 subgroup; 35% of patients overall had undocumented/UNK disease sidedness. ^cOverall, 8% of patients had a primary tumor in the rectosigmoid junction. ^dOverall, 11% of patients had lymph node metastases, 4% had ovary metastases, and 9% had undocumented/UNK metastases. ^eOverall, 11% and 8% of patients received FOLFOXIRI/FOLFIRINOX or other chemotherapy, respectively.
CMS, consensus molecular subtype; UNK, unknown.

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Methods

- This retrospective observational study leveraged the Tempus multimodal clinicogenomic database to identify patients with RAS/RAF WT MSS mCRC treated with 1L anti-EGFR therapy (cetuximab or panitumumab) plus fluorouracil-based chemotherapy (Figure 1)
- CMS classification was assigned using the CMScaller algorithm applied to RNA sequencing data from a qualifying biopsy near 1L treatment initiation
- Real-world overall survival (rwOS) and real-world progression-free survival (rwPFS) were measured from 1L treatment initiation and evaluated using time-varying Cox proportional hazards models adjusted for the presence of liver/peritoneum metastases and chemotherapy backbone, with CMS as the primary covariate

Figure 1: Study design

Timeline diagram illustrating the study design:

- Primary diagnosis date: primary diagnosis of CRC with age at diagnosis 18–89 years
- Baseline period spans from patient's first record in the database to the index date
- Baseline clinical characteristics, ±60 days of index date, unless otherwise specified
- LoT: Anti-EGFR + chemo
- Sample collected for biomarker testing, ≤30 days post LoT1, where LoT1 is the anchor
- Qualifying biopsy period^a
- Progression from LoT1
- Follow-up period spans from index date to last known date in the patient record
- Death
- Tempus + third-party death sources

^aIf a patient had multiple biopsies within the qualifying biopsy period, the biopsy closest to the anchor was selected as the qualifying biopsy. The qualifying biopsy was used to determine the RAS/RAF/MSI status and CMS classification.
CMS, consensus molecular subtype; LoT, line of therapy; MSI, microsatellite instability.

Distribution of CMS classifications

- Distribution of CMS classifications was generally consistent with the literature⁵ (Figure 3A)
 - Fewer patients had CMS1 and CMS3 tumors compared with other subtypes due to the biologic features of these subtypes and the required biomarker status for inclusion in these cohorts (RAS/BRAF WT and MSS)
 - About 13% of patients had a CMS classification that could not be clinically reported (CMS unknown), which potentially reflects technical limitations of RNA-based classification, low-confidence classification, or mixed molecular features
- There was a significant difference in the distribution of both liver and peritoneal metastases between CMS2 and CMS4 classifications ($P<0.001$; Figures 3B and 3C)
 - Patients with CMS2 tumors had a higher prevalence of liver metastases (Figure 3B)

Figure 3: Distribution of CMS classifications and liver metastases

Figure 3 displays the distribution of CMS classifications and liver metastases:

- A. Overall population (n=238)**: CMS1 (13%), CMS2 (48%), CMS3 (7%), CMS4 (32%), CMS UNK (<1%)
- B. CMS2 (n=114)**: UNK (8%), No liver metastases (19%), Any liver metastases (73%)
- C. CMS4 (n=77)**: UNK (9%), No liver metastases (35%), Any liver metastases (56%)

CMS, consensus molecular subtype; UNK, unknown.

Figure 5: CMS2 versus CMS4 (A) rwOS and (B) rwPFS

Figure 5 displays survival outcomes for CMS2 versus CMS4:

- A. Median rwOS (95% CI)**: CMS2 31.3 mo (26.8–40.3), CMS4 24.4 mo (18.8–28.5). HR, 0.57 (95% CI, 0.35–0.91)
- B. Median rwPFS (95% CI)**: CMS2 14.6 mo (11.4–17.0), CMS4 11.7 mo (9.0–15.1). HR, 0.74 (95% CI, 0.49–1.13)

Note: Time-varying Cox proportional hazards models were used to assess rwOS and rwPFS.
CMS, consensus molecular subtype; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

Solid Tumors

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