Journal of Cancer Research and Practice

journal homepage: https://journals.lww.com/jcrp

Case Report

Acquired Resistance in BRAF V600E-Mutant MSS Colorectal Cancer: Two Cases Highlighting Molecular Adaptation and Salvage Strategies

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Abstract

BRAF V600E mutations in metastatic colorectal cancer (mCRCs) are associated with aggressive tumor behavior and poor prognosis, with limited benefit from BRAF inhibitors due to rapid resistance mechanisms. Here, we report the two cases of microsatellite-stable, BRAF V600E-mutated mCRC demonstrating resistance to multiple lines of therapy, including BRAF/epidermal growth factor receptor inhibition. In both cases, comprehensive molecular profiling identified co-occurring mutations associated with immune escape and pathway reactivation. Rational off-label therapeutic combinations of regorafenib plus nivolumab in one patient and dabrafenib, trametinib and cetuximab in the other were associated with clinical benefit. These cases highlight the role of serial molecular reassessment and individualized treatment strategies for patients with BRAF V600E-mutant mCRC.

Keywords: BRAF V600E, case report, immunotherapy, metastatic colorectal cancer, regorafenib, targeted therapy resistance

Introduction

BRAF V600E mutations occur in approximately 8%–10% of metastatic colorectal cancer (mCRC) and are associated with right-sided location, poor response to standard therapy, and unfavorable outcomes.[1] Despite initial success in melanoma, BRAF inhibitors have limited efficacy in colorectal cancer (CRC) due to epidermal growth factor receptor (EGFR)-mediated mitogen-activated protein kinase (MAPK) reactivation and alternative resistance mechanisms. The BEACON CRC trial established dual BRAF and EGFR inhibition with encorafenib and cetuximab as standard of care in previously treated patients.[2] Recently, the phase III BREAKWATER trial extended this strategy to first-line therapy, showing significantly improved survival outcomes.[3] However, resistance remains inevitable. Here, we report the two cases of microsatellite-stable (MSS), BRAF

Submitted: 30-Jul-2025 **Revised:** 26-Aug-2025
Accepted: 23-Sep-2025 **Published:** 20-Jan-2026

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-25-00041

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How to cite this article: Lin WY, Chen MH. Acquired resistance in BRAF V600E-Mutant MSS colorectal cancer: Two cases highlighting molecular adaptation and salvage strategies. J Cancer Res Pract 2026;13:38-42.

V600E-mutated mCRC demonstrating resistance to multiple lines of therapy. These cases illustrate the molecular drivers of resistance and salvage responses to off-label targeted combinations.[4,5]

Case Reports

Case 1

A 54-year-old woman was diagnosed with BRAF V600E-mutant MSS adenocarcinoma of the cecum (pT3N2b) in January 2022. She underwent right hemicolectomy, followed by four cycles of adjuvant mFOLFOX6. However, metastatic disease developed shortly thereafter. Over the next 2 years, she received multiple lines of therapy, including FOLFIRI-bevacizumab, capecitabine-bevacizumab maintenance, two courses of chemoradiotherapy, XELOX, and targeted combinations including encorafenib plus cetuximab [Figure 1].

Despite ongoing treatment with encorafenib, cetuximab, and oral UFUR, her tumor markers rose sharply. A FoundationOne® Liquid CDx assay, submitted on March 12, 2025, identified a persistent BRAF V600E mutation, along with several acquired somatic alterations suggesting resistance mechanisms. High variant allele frequencies (Variant Allele Frequency [VAF] >45%) were observed in AXIN1 (p.S768L), NOTCH1 (p.D1994N), TSC1 (p.S457R), and P2RY8 (p.E323G), while low VAF variants (<1%) were detected in KIT (p.F63 L), NTRK1 (p.M638K), PTEN (p.M205V), RB1 (p.R798Q), DNMT3A (p.F755V), and BCOR (p.A570T) [Table 1]. This mutation pattern suggested clonal evolution and potential bypass activation of downstream or parallel oncogenic pathways.

In light of her clinical deterioration and molecular evidence of acquired resistance, she was started on a combination regimen of regorafenib and nivolumab in May 2025. Remarkably, this treatment led to a sustained decline in carcinoembryonic antigen, representing the first favorable tumor marker response since the onset of resistance. The combination was well tolerated, with no significant immune-related adverse events or dose-limiting toxicities.

Case 2

A 56-year-old woman with MSS, BRAF V600E-mutant right-sided colon cancer and synchronous liver metastases underwent hemicolectomy and liver resection in October 2022. She was initially treated with encorafenib plus cetuximab, followed by multiple lines including FOLFOXIRI-bevacizumab (with radiofrequency ablation), FOLFIRI-bevacizumab, and immunotherapy-based regimens (nivolumab with cetuximab, paclitaxel, or sacituzumab govitecan). However, the paclitaxel and sacituzumab combinations were discontinued after only 1–2 cycles due to acute hypersensitivity reactions, including chest tightness, flushing, and poor tolerability, while nivolumab monotherapy was continued as part of subsequent treatment strategies [Figure 2].

A contrast-enhanced computed tomography scan in February 2025 revealed marked disease progression, with right pleural seeding, recurrent hepatic metastases, peritoneal carcinomatosis with ascites, and extensive lymphadenopathy. A comprehensive reassessment using the AVENIO tumor tissue comprehensive genomic profiling (CGP) Panel, performed on a skin biopsy obtained on January 21, 2025, confirmed a persistent BRAF V600E mutation and identified multiple additional genomic alterations: BRCA2 p.S1946* and TP53 p.Q331*, both truncating mutations. Additional mutations of uncertain significance were found in FANCG (p.R141C), DAXX (p.P627S), PTCH1 (p.P1318 L), MYCN (p.A215V), ASXL1 (p.D832E), and TET2 (p.F662V) [Table 2]. The tumor mutational burden remained low.

In light of this molecular profile, the patient was initiated on a targeted combination regimen comprising dabrafenib, trametinib, and cetuximab on February 19, 2025. Although interval imaging could not be obtained due to a rapid clinical

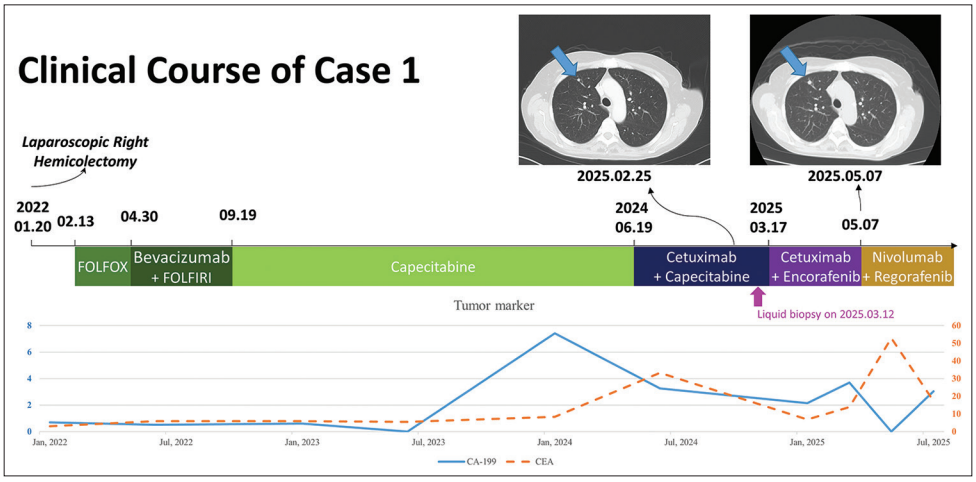

Figure 1: Timeline of treatment and disease status in case 1. A chronological overview showing treatment regimens, serial carcinoembryonic antigen trends, and key imaging findings in a patient with BRAF V600E–mutant, microsatellite-stable metastatic colorectal cancer. The plot highlights clinical progression, therapeutic resistance, and subsequent biochemical response following the initiation of regorafenib and nivolumab. The blue arrows indicate tumor progression after treatment

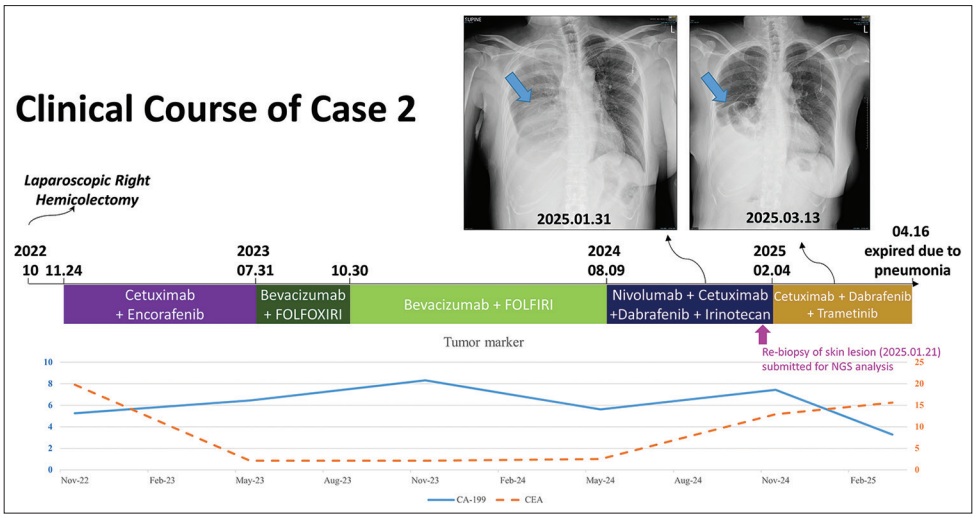

Figure 2: Timeline of treatment and disease status in case 2. A longitudinal depiction of systemic therapies, disease progression, and clinical findings in a patient with BRAF V600E–mutant, microsatellite-stable metastatic colorectal cancer. The figure shows multiple lines of targeted, cytotoxic, and immunotherapeutic regimens, culminating in a short-lived clinical improvement following the initiation of dabrafenib, trametinib, and cetuximab. Notable clinical changes included regression of cutaneous metastases and resolution of the pleural effusion, highlighted by blue arrows

decline, notable clinical improvements were observed, including a reduction in cutaneous subcutaneous nodules and resolution of pleural effusion. Although tumor markers stabilized, there was no substantial decline. The patient ultimately succumbed to progressive dyspnea and pulmonary infection, leading to respiratory failure.

Discussion

BRAF V600E mutations drive constitutive MAPK pathway activation and occur in approximately 8%–10% of mCRC.[6] These tumors are clinically aggressive, often right-sided, and associated with a poor response to conventional cytotoxic regimens. Unlike in melanoma, where BRAF inhibition yields high response rates, resistance in CRC emerges rapidly due to tumor-intrinsic and microenvironmental features – most notably, EGFR-mediated reactivation of the MAPK pathway and bypass activation of phosphoinositide 3-kinase (PI3K)–AKT (protein kinase B, PKB) signaling.

The BEACON CRC trial showed that dual inhibition of BRAF and EGFR modestly improved progression-free and overall survival compared to standard chemotherapy.[2] More recently, the BREAKWATER trial suggested that the addition of encorafenib and cetuximab to first-line FOLFOX may offer significant benefit.[3] Nonetheless, acquired resistance remains nearly universal, often within 6–12 months, and optimal sequencing or salvage strategies have not been established.

Our two cases demonstrate the distinct clinical courses of patients with MSS, BRAF V600E–mutated mCRC who progressed despite multiple lines of systemic therapy, including targeted agents. In both cases, comprehensive molecular profiling at the time of progression provided critical insights into potential mechanisms of resistance and helped guide therapeutic decisions beyond conventional standards.

Post hoc analysis of the BEACON CRC study has identified several molecular features associated with resistance to BRAF and EGFR inhibition, such as RAS mutations, EGFR amplification, and alterations in the PI3K pathway.[7] This highlights the importance of re-assessing the evolving genomic landscape at disease progression. Moreover, a more recent molecular correlation analysis from the BEACON study[8] reported that resistance-associated alterations were commonly found in patients with limited clinical benefit to targeted regimens, underscoring the need for timely and comprehensive next-generation sequencing to inform personalized salvage strategies.

In Case 1, the disease initially responded to encorafenib and cetuximab but subsequently progressed despite the addition of oxaliplatin, irinotecan, and fluoropyrimidines. A FoundationOne® Liquid CDx assay performed at the time of progression revealed a persistent BRAF V600E mutation and multiple co-occurring alterations, including high VAF mutations in TSC1 (S457R), AXIN1 (S768 L), NOTCH1 (D1994N), and P2RY8 (E323G). These mutations may represent clonal adaptations that enabled therapeutic escape. For example, TSC1 loss has been shown to disrupt mechanistic target of rapamycin (mTOR) regulation and enhance interferon signaling and increase tumor immunogenicity in other cancer types.[9] The AXIN1 mutation, a negative regulator of the Wnt pathway, may allow reactivation of β-catenin–mediated immune exclusion.[10] These events, coupled with subclonal alterations in PTEN and RB1, likely create a genetically heterogeneous, immune-resistant tumor microenvironment.[11,12]

Notably, although prior *post hoc* analyses of the BEACON trial identified RAS or MEK1 mutations as common resistance drivers under dual BRAF/EGFR inhibition, neither alteration was found in our case. This suggests that noncanonical pathways such as PI3K/mTOR dysregulation

Table 1: Comprehensive genomic profiling results of case 1

Category	Gene/biomarker	Variant	VAF%
Biomarker findings	TMB	6 Muts/Mb	-
	MSI	MSI-high not detected	-
	ctDNA tumor fraction	High (1.1%)	-
Genomic findings	BRAF	V600E	0.78
	APC	E1286*	1.2
	DNMT3A	R882C	1.3
		F755V	3.8
	TNFAIP3	C579fs*93	0.36
	TP53	G245S	0.20
		E258K	1.2
	AXIN1*	p.S768L	50.8
	BCOR	p.A570T	0.36
	KIT	p.F63L	0.37
	NOTCH1*	p.D1994N	47.8
	NTRK1	p.M638K	0.59
	P2RY8*	p.E323G	48.5
	PTEN	p.M205V	0.62
	RB1	p.A2393G	0.7
	TSC1*	p.S457R	49.9

*Variants marked with an asterisk indicate relatively high (VAF >30%), suggesting potential clonal dominance or biologically significant subpopulations. TMB: Tumor mutational burden, MSI: Microsatellite instability, VAF: Variant allele frequency

Table 2: Comprehensive genomic profiling results of case 2

Category	Gene/biomarker	Variant	VAF (%)
Biomarker findings	TMB	8.44 muts/Mb	-
	MSI	MSS	-
	Genomic LOH	Undetermined	-
Genomic findings	BRAF	p.V600E	43
	BRCA2*	p.S1946*	60
	TP53*	p.q331*	50
	BRAF	(exon 2–10) deletion	7.28
	AXIN1	c. 1019+1G>T	34
	IRS2*	p.P813S	85
	TP53BP1	p.Q1813fs	16

*Variants marked with an asterisk indicate relatively high (VAF >30%), suggesting potential clonal dominance or biologically significant subpopulations. VAF: Variant allele frequency, TMB: Tumor mutational burden, MSI: Microsatellite instability, LOH: Loss of heterozygosity, MSS: Microsatellite stable

or Wnt pathway reactivation may also mediate therapeutic escape in BRAF V600E–mutant MSS mCRC. Our findings expand the spectrum of possible resistance mechanisms and underscore the need for individualized profiling beyond the classical MAPK axis.

Despite prior exposure to chemotherapy, radiotherapy, and targeted therapies, the patient had a notable biochemical and clinical response to regorafenib plus nivolumab, a combination previously shown to have limited efficacy in unselected MSS CRC. Regorafenib has immunomodulatory properties including inhibition of CSF1R and VEGFR, reduction of M2 macrophage polarization, and increased tumor susceptibility to immune effector cells. In this molecular context – marked by immunogenic stress, disrupted Wnt and mTOR signaling, and clonal reshaping – the tumor may have shifted toward an inflamed phenotype, allowing checkpoint inhibition to exert delayed activity.

In Case 2, the patient similarly progressed after multiple regimens, including upfront BRAF-targeted therapy, antiangiogenic agents, and immunotherapy. At the time of widespread disease progression with pleural, peritoneal, and hepatic involvement, AVENIO Tumor Tissue CGP analysis identified BRCA2 p.S1946* and TP53 p.Q331* truncating mutations along with BRAF V600E.[13] These alterations, while not traditionally associated with MAPK resistance, may contribute to genomic instability and therapeutic escape through disruption of DNA damage repair and cell cycle regulation. Although the tumor mutation burden was low, the presence of biallelic inactivation of TP53 and BRCA2 suggested possible vulnerability to cytotoxic or stress-response–targeting strategies.[14]

Based on these findings and the absence of standard options, the patient was initiated on dabrafenib, trametinib, and cetuximab. Although clinical deterioration precluded interval imaging, resolution of pleural effusion and regression of cutaneous metastatic nodules were observed, suggesting an effect on disease course. This regimen, while not standard in CRC, has shown preclinical and anecdotal activity in tumors with co-occurring BRAF mutations and TP53 or BRCA pathway alterations, where combined MAPK inhibition and EGFR blockade may prevent feedback activation and enhance therapeutic durability. Again, despite the absence of RAS or MEK1 mutations – the most commonly reported mechanisms of acquired resistance in the BEACON study – this case revealed other potentially relevant alterations such as TP53 and BRCA2 loss, implicating genome instability and altered cell death signaling as plausible escape pathways.

These two cases underscore several key principles. First, BRAF-mutated mCRC is biologically distinct from its melanoma counterpart and requires context-specific therapeutic strategies. Second, clonal evolution and pathway bypass mechanisms play central roles in resistance and can be revealed through serial molecular profiling. Third, immunotherapy, even in MSS tumors, may be beneficial when combined with microenvironment-modulating agents such as regorafenib, particularly in the presence of sensitizing mutations such as TSC1 or AXIN1. Finally, rare combinations such as dabrafenib/trametinib/cetuximab may merit consideration in molecularly selected, treatment-refractory patients.

Conclusion

These two cases illustrate the therapeutic challenges and heterogeneity of resistance mechanisms in BRAF V600E–mutant, MSS mCRC. While dual BRAF and EGFR inhibition

remains a cornerstone of treatment, resistance is inevitable. Comprehensive molecular profiling at the time of progression can reveal the potential mechanisms of resistance, such as mutations in TSC1, AXIN1, or BRCA2, and guide rational off-label or experimental therapeutic combinations. The observed clinical benefits from regorafenib plus nivolumab and from dabrafenib/trametinib/cetuximab suggests that leveraging molecular vulnerabilities – even in nonstandard combinations may offer valuable salvage options for this difficult-to-treat population.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgments

The authors thank the Molecular Tumor Board (MTB) team at Taipei Veterans General Hospital for their insightful discussions and multidisciplinary input that contributed to the clinical decision-making process in both cases.

Author contributions

Wen-Ying Lin conceived the case report, collected clinical data and images, performed the literature review, and drafted the manuscript. Ming-Huang Chen supervised clinical management, verified the clinical and pathological findings, provided critical revisions for important intellectual content, and approved the final version. Both authors approved the final manuscript and agree to be accountable for all aspects of the work.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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