Glimmers of Hope—New Strategies for Overcoming Treatment Resistance in Patients with *BRAF* V600E-mutated Metastatic Colorectal Cancer

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BRAF V600E-mutated metastatic colorectal cancer is notoriously difficult to treat due to an aggressive tumor biology and resistance to chemotherapy. Single-agent BRAF inhibition has proven ineffective in this patient population. Approaches combining BRAF with epidermal growth factor receptor and mitogen-activated extracellular signal-regulated kinase inhibition are effective in overcoming resistance to BRAF monotherapy, and this treatment combination provides a superior overall survival benefit compared with irinotecan-based chemotherapy. Encorafenib plus cetuximab is now a US Food and Drug Administration-approved treatment option for patients with *BRAF* V600E-mutated metastatic colorectal cancer after prior therapy. Ongoing clinical trials using immunotherapy and other targeted agents aim to further improve on these outcomes. We highlight the epidemiology and mutational landscape of *BRAF*-mutated colorectal cancer, as well as novel treatment options for patients with this subtype of metastatic colorectal cancer.

Keywords

Colorectal cancer, BRAF, *BRAF*-V600E mutation, targeted therapy

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Colorectal cancer (CRC) is a commonly diagnosed malignancy and the second-leading cause of cancer death in the USA, with 147,950 estimated new cases and 53,200 estimated deaths in 2020.[1] Despite CRC screening, approximately 20% of patients are diagnosed with metastatic CRC (mCRC), which carries a 14.2% 5-year survival rate.[2]

Over the last two decades, mCRC treatment has become more personalized, with a better understanding of tumor heterogeneity, including microsatellite instability (MSI) and mutations in genes such as *KRAS*, *NRAS*, and *BRAF*. The availability of molecularly tailored treatments has reshaped the therapeutic landscape for many patients with mCRC. Approximately 8–12% of mCRCs contain a mutation in *BRAF*, also known as v-raf murine sarcoma viral oncogene homolog B.[3–6] BRAF is a signal transduction protein involved in the mitogen-activated protein kinase (MAPK) pathway.[3] Here we review the prognostic and therapeutic implications of *BRAF*-mutated CRC.

BRAF pathway and mutations in malignancies

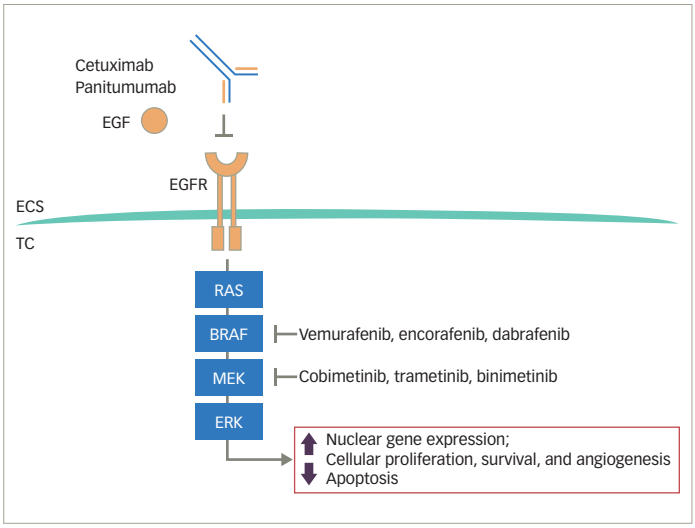
The *BRAF* gene is located on chromosome 7 (7q34). It encodes the BRAF protein, a serine/threonine protein kinase, which plays a role in the regulatory MAPK/extracellular signal-regulated kinase (ERK) signaling pathway during cell growth, proliferation, differentiation, and apoptosis.[7,8] Mutations in *BRAF* result in downstream phosphorylation of mitogen-activated extracellular signal-regulated kinase (MEK) and ERK, leading to activation of the MAPK pathways. This oncogenic mutation stimulates cell proliferation and metastasis (*Figure 1)*.

BRAF mutations have been identified with varying incidence in multiple malignancies, including melanoma, CRC, hairy cell leukemia, lung cancer, ovarian cancer, Langerhans cell histiocytosis, and papillary thyroid carcinoma.[9–14] The BRAF inhibitors, dabrafenib, encorafenib, and vemurafenib, are US Food and Drug Administration (FDA)-approved therapies for patients with *BRAF*-mutated melanoma. Median progression-free survival (PFS) of patients with melanoma treated with these inhibitors ranges from 5–10 months.[15–18]

BRAF mutations in colorectal cancer

Most *BRAF* mutations in CRC appear in primary tumors located in the proximal colon and first two-thirds of the transverse colon. *BRAF*-mutated tumors tend to be larger than average, are associated with serrated polyp morphology, and have higher rates of distant metastases.[19] Eighty percent of hyperplastic microvascular polyps harbor *BRAF* mutations, and these polyps present in the proximal

Figure 1: Mechanisms of action of agents targeting *BRAF* V600E-mutated metastatic colorectal cancer



ECS = extracellular space; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; ERK = extracellular signal-regulated kinase; MEK = mitogen-activated extracellular signal-regulated kinase; TC = tumor cell.

colon as sessile serrated adenomas.[19] These types of polyps have high malignant potential and are under-detected by conventional colonoscopies, leading to their ability to progress without being detected.[19] *BRAF*-mutated CRCs metastasize readily to the peritoneum and distant lymph nodes, but less readily to the lungs. *BRAF* mutations occur more commonly in mCRCs that are microsatellite instable. Women and individuals over the age of 65 years are more likely to have mCRCs that harbor mutated *BRAF*.[5,20]

In response to the binding of extracellular growth factors, receptor tyrosine kinases activate RAS, which activates and induces the formation of RAF dimers to propagate and transduce downstream signaling to promote cell proliferation and differentiation. Mutations in *BRAF* fall into one of three categories based on the biochemical and signaling properties of their encoded proteins. Class 1 contains the most common *BRAF* mutation known as *BRAF* V600E, which is the product of a thymine to adenine base transversion at codon 600 of exon 15 of *BRAF*. This mutation, which leads to a substitution of valine for glutamate at position 600 of the encoded protein, is observed in approximately 10% of all patients with mCRC and accounts for around 80% of all *BRAF* mutations.[21] The resulting aberrant protein exhibits high kinase activity and can signal independently of RAS activation.[21] *BRAF* mutations in classes 2 and 3 occur at different locations in the *BRAF* gene, encoding non-V600E mutated proteins. These non-V600E *BRAF* mutations are observed in mCRCs of approximately 2% of patients and account for around 20% of all *BRAF* mutations (about 10% in each of class 2 and 3).[21] Class 2 mutations, like class 1, give rise to proteins that signal independently of RAS. In contrast, class 3 *BRAF* mutations encode proteins that have enhanced binding to RAS and CRAF and lead to RAS-dependent signaling.[6]

The activities of these different classes of *BRAF* mutations correlate with differences in the clinical characteristics of *BRAF*-mutant mCRC and response to targeted therapy. Tumors with class 1 *BRAF* mutations (*BRAF* V600E-mutant) are typically found in right-sided, high-grade, MSI-high tumors and are associated with a worse patient prognosis compared with *BRAF*-wild type (WT) tumors. Patients with *BRAF* V600E-mutated mCRC have a median overall survival of 4–6 months after failure of initial therapy, compared with 11–14 months for all patients with mCRC.[22,23] Class 2 and 3 (*BRAF* non-V600E mutant) tumors have been observed in younger patients with left-sided tumors, and the prognosis for these patients is similar to those with *BRAF*-WT tumors.[6]

The class of *BRAF* mutation is clinically relevant because it has been shown to indicate prognosis, as well as effectiveness of the BRAF inhibitors, vemurafenib, dabrafenib, and encorafenib, and the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies, cetuximab and panitumumab.[22,23] Upon further examination of clinical characteristics of CRC tumors with non-V600E *BRAF* mutations, patients with *RAS*-WT tumors and class 2 *BRAF*-mutated CRC had shorter survival compared with those with *RAS*-WT and class 3 *BRAF*-mutant CRC.[25] EGFR is a receptor tyrosine kinase in the MAPK pathway; RAS and BRAF operate downstream of EGFR.[6] While EGFR inhibitors improve overall survival in CRC, CRC tumors with activating *RAS* mutations do not benefit from treatment with anti-EGFR antibodies.[24] Because class 1 *BRAF* mutations are RAS activating, anti-EGFR antibody monotherapy is ineffective. Similarly, class 2 *BRAF*-mutant CRCs rarely respond to EGFR therapy, suggesting that class 2 *BRAF* mutations confer resistance.[25] Of 36 patients with non-V600E *BRAF* mutations, patients with class 2 and 3 BRAF mutations did not have any objective response to anti-EGFR monotherapy.[26] Class 3 mutated CRCs that did not respond to anti-EGFR therapy have been shown to be linked to underlying activation of other receptor tyrosine kinases leading to RAS activation.[25] However, considering that a large portion of patients with class 3 *BRAF* mutations responded to anti-EGFR therapy, the main driver in these tumors is thought to be EGFR activation. These patients likely have tumors that are sensitive to EGFR inhibition.[26]

Treatment in *BRAF* V600E-mutated CRC

Patients with *BRAF* V600E-mutated CRC currently have shorter PFS on chemotherapy, an increased rate of disease recurrence after surgical resection, and poorer overall survival.[20,27] As mentioned above, *BRAF* mutations in CRC confer resistance to anti-EGFR therapy,[28–32] and tend to be refractory to standard chemotherapy.[33] Upfront intensive chemotherapy is often used, based on the phase III TRIBE trial results (ClinicalTrials.gov identifier: NCT00719797), which observed benefit of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI)/bevacizumab over fluorouracil, leucovorin, and irinotecan (FOLFIRI)/bevacizumab in patients with *BRAF*-mutated mCRC.[34] In the TRIBE2 trial (ClinicalTrials.gov identifier: NCT02339116), which included 10% *BRAF*-mutated patients in each arm, the combination of FOLFOXIRI/bevacizumab improved PFS during both upfront and pre-planned re-introduction after disease progression, as well as longer overall survival (27.6 versus 22.6 months, hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.67–0.98, p=0.033).[35]

Although the *BRAF* V600E mutation has been identified and successfully targeted in multiple other advanced cancers, *BRAF*-inhibitor monotherapy shows limited efficacy in cases of *BRAF* V600E-mutated mCRC. Vemurafenib is a small tyrosine kinase inhibitor that specifically targets the adenosine triphosphate-binding domain of *BRAF* V600E, and has been shown to decrease activation of the MAPK pathway in advanced malignancies with *BRAF* mutations.[4] In mCRC, vemurafenib monotherapy is rarely effective at reducing tumor growth. This decreased efficacy is attributed to incomplete inhibition of MAPK signaling and a reflexive activation of EGFR, which promotes tumor progression through alternative pathways,

Table 1: Ongoing clinical trials in patients with *BRAF*-mutated colorectal cancer

NCT identifier	Title	Trial drug(s)	Target	Phase	Study size (N)
NCT04294160	A Study of Select Drug Combinations in Adult Patients With Advanced/ Metastatic *BRAF* V600 Colorectal Cancer	Dabrafenib	BRAF	I	280
		LTT462	ERK		
		Trametinib	MEK		
		LXH254	BRAF		
		TNO155	SHP2		
		Spartalizumab	PD-1		
NCT03693170	Encorafenib, Binimetinib and Cetuximab in Subjects With Previously Untreated *BRAF*-mutant ColoRectal Cancer (ANCHOR-CRC)	Encorafenib	BRAF	II	95
		Binimetinib	MEK		
		Cetuximab	EGFR		
NCT03727763	Cetuximab and Vemurafenib Plus FOLFIRI for *BRAF* V600E Mutated Advanced Colorectal Cancer (IMPROVEMENT)	Vemurafenib	BRAF	II	30
		Cetuximab	EGFR		
NCT02164916	S1406 Phase II Study of Irinotecan and Cetuximab With or Without Vemurafenib in *BRAF* Mutant Metastatic Colorectal Cancer	Cetuximab	EGFR	II	106
		Irinotecan hydrochloride			
		Vemurafenib	BRAF		
NCT02906059	Study of Irinotecan and AZD1775, a Selective WEE1 Inhibitor, in *RAS* or *BRAF* Mutated, Second-line Metastatic Colorectal Cancer	AZD1775 Irinotecan	WEE1	I	32
NCT04034459	FOLFOXIRI Plus Cetuximab versus FOLFOXIRI Plus Bevacizumab 1st-line in *BRAF*-mutated mCRC (AIO-KRK-0116)	Bevacizumab	VEGF	II	99
		Irinotecan			
		Folinic acid			
		Oxaliplatin			
		5-Fluorouracil			
		Cetuximab	EGFR		
NCT01750918	BRAF/MEK/EGFR Inhibitor Combination Study in Colorectal Cancer (CRC)	Dabrafenib	BRAF	I/II	170
		Trametinib	MEK		
		Panitumumab	EGFR		
		5-Fluorouracil			
NCT03668431	Dabrafenib + Trametinib + PDR001 in Colorectal Cancer	Dabrafenib	BRAF	II	25
		Trametinib	MEK		
		PDR001 (spartalizumab)	PD-1		
NCT04017650	Encorafenib, Cetuximab, and Nivolumab in Treating Patients With Microsatellite Stable, *BRAF* V600E Mutated Unresectable or Metastatic Colorectal Cancer	Cetuximab	EGFR	I/II	38
		Encorafenib	BRAF		
		Nivolumab	PD-1		
NCT01351103	A Study of LGK974 in Patients With Malignancies Dependent on Wnt Ligands	LGK974	Wnt pathway	I	170
		PDR001 (spartalizumab)	PD-1		

This table summarizes clinical trials that are not yet recruiting, recruiting, or active and no longer recruiting and pending result reporting. The studies were captured from ClinicalTrials.gov on March 25, 2020. EGFR = epidermal growth factor receptor; ERK = extracellular signal-regulated kinase; FOLFIRI = fluorouracil, leucovorin, and irinotecan; FOLFOXIRI = fluorouracil, leucovorin, oxaliplatin, and irinotecan; mCRC = metastatic colorectal cancer; MEK = mitogen-activated extracellular signal-regulated kinase; NCT = National Clinical Trial; PD-1 = programmed cell death protein 1; SHP2 = Src homology 2-containing phosphotyrosine phosphatase; VEGF = vascular endothelial growth factor.

bypassing *BRAF*.[4] The combination of vemurafenib plus trametinib (a MEK inhibitor) resulted in response rates as high as 76% in *BRAF* V600E-mutated metastatic melanoma. In contrast, this same combination yielded only a 12% response rate in *BRAF* V600E-mutated CRC.[36] In a phase IB study of 17 patients with *BRAF* V600E-mutated mCRC, the addition of vemurafenib to a combination of irinotecan plus cetuximab yielded a 35% response rate and a median PFS of 7.7 months.[4] Patients with radiographically observed responses and stable disease also exhibited reductions in the percentage of *BRAF* V600E cell-free DNA.[4]

This regimen was further studied in the phase II SWOG S1406 study (ClinicalTrials.gov identifier: NCT02164916), which randomized patients with previously treated *BRAF* V600E-mutated mCRC 1:1 to irinotecan plus cetuximab versus irinotecan plus cetuximab and vemurafenib. The primary endpoint of PFS was significantly longer in the arm that received vemurafenib: 4.3 versus 2.0 months (HR 0.48, 95% CI 0.31–0.75; p=0.001).[22]

In addition to combined inhibition of EGFR and BRAF, the inhibition of the MAPK pathway has been explored through the combined inhibition of the MEK, EGFR, and BRAF. The phase III BEACON study (ClinicalTrials.gov identifier: NCT02928224) randomized patients with previously treated *BRAF* V600E-mutated mCRC 1:1:1 to triplet therapy with encorafenib (BRAF inhibitor), cetuximab (anti-EGFR antibody), and binimetinib (MEK inhibitor); doublet therapy with encorafenib and cetuximab; or the control arm of

chemotherapy (FOLFIRI or irinotecan) with cetuximab (N=665).[37] Patients treated with the triplet and doublet therapy had significantly longer median overall survival when compared with the control arm: 9.3 and 9.3 versus 5.9 months, respectively. The median overall response rate was also higher with the triplet (27%) and doublet (20%) therapy compared with the control arm of chemotherapy (2%, p<0.0001).[37] As there was not a significant difference in overall survival between the triplet and doublet therapies, doublet therapy with encorafenib and cetuximab received FDA approval for patients with *BRAF* V600E-mutated mCRC after prior therapy on April 8, 2020.[38] This study's quality-of-life assessment revealed the doublet and triplet regimens were not different, but both regimens provided improved patient-reported quality of life compared with the control arm.[39] The ongoing phase III ANCHOR trial is evaluating the triplet therapy in the first-line setting (ClinicalTrials.gov Identifier: NCT03693170).

Future approaches to treating *BRAF*-mutated CRC

While *BRAF* V600E mutations are currently a poor prognostic marker, the use of targeted therapies as well as high prevalence of MSI-high, which lends potential benefit from checkpoint inhibitors, are promising therapeutic avenues. Future clinical trials are accruing patients with *BRAF*-mutated CRC to test multi-agent combinations that inhibit various signaling proteins along the MAPK pathway. Novel targeted agents include ERK inhibitors, e.g., LTT462; BRAF inhibitors, e.g., LXH254; Src homology 2-containing phosphotyrosine phosphatase (SHP2) inhibitors, e.g., TNO155; WEE1 kinase inhibitors, e.g., AZD1775; and Wnt inhibitors, e.g., LGK974 (*Table 1*). These novel agents are being combined together, added to traditional chemotherapy as well as immunotherapy, in the hope of overcoming the treatment resistance conferred by *BRAF* mutations. One phase Ib clinical trial is utilizing combinations of targeted agents in the hope to prove the safety of combinations, as well as overcoming potential downstream resistance mechanisms (ClinicalTrials.gov identifier: NCT04294160). Novel combinations include a doublet BRAF inhibitor with ERK inhibitor; triplet arms that include a BRAF inhibitor, ERK inhibitor, and MEK inhibitor; and targeted agents plus immunotherapy or chemotherapy to review safety as well as efficacy.

The utilization of concomitant MSI and *BRAF* mutation testing may help predict response to checkpoint inhibition. Triplet combinations of BRAF inhibition, MEK inhibition, and programmed cell death protein 1 (PD-1) inhibition have been tested on *BRAF*-mutated melanomas in the phase III COMBI-i trial with acceptable safety profiles and promising response rates.[40] This same combination is being testing in *BRAF*-mutated CRC (ClinicalTrials.gov identifier: NCT03668431). Given its recent FDA approval, encorafenib and cetuximab will likely form the backbone of future studies combining anti-BRAF/EGFR therapy with chemotherapy and other targeted agents.

Radiological studies have also explored the use of imaging factors to predict which patients are more likely to have a *BRAF* mutation in their tumors. One study (N=155) showed *BRAF* mutations were more common in female patients (p=0.007), older patients (p=0.001), and right-sided tumors (p=0.001).[38] Radiologically significant factors seen in *BRAF*-mutated tumors, as opposed to *BRAF*-WT tumors, included right-sidedness (p=0.002); heterogeneous enhancement, possibly due to association between *BRAF* and a mucinous histology (p=0.039); and lack of non-peritoneal metastases (p=0.043).[41]

In addition to adenocarcinoma CRC, *BRAF* V600E mutations have recently been identified in colon neuroendocrine tumors at rates as high as 28% and may benefit from targeted therapy as well.[35] This population has unique and complex biological differences compared with *BRAF*-mutated CRC adenocarcinoma as well as melanoma and will need to be tested in basket trials.

Conclusion

BRAF mutations in mCRC have traditionally portended a poor prognosis and decreased benefit from standard therapies. Although recent studies have shown improved overall survival and response rates with combined encorafenib and cetuximab, there is still a need to identify novel therapy combinations that can further extend survival outcomes of *BRAF*-mutated patient populations. ❑

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