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ABOUT COVER

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MINIREVIEWS

Contemporary treatment approaches for metastatic colorectal cancer driven by *BRAF* V600 mutations

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Abstract

The treatment of metastatic colorectal cancer (mCRC) harboring *BRAF* V600 mutations is challenging. These tumors are often refractory to standard treatment. Therefore, the patients may exhibit rapid clinical deterioration, depriving them of the chance to receive salvage therapy. In newly diagnosed patients with good performance status, the administration of an intensive chemotherapy regimen like FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) along with the antiangiogenic agent bevacizumab can modify this aggressive behavior of the disease and improve patient clinical outcomes. The recently published results of the BEACON (Binimetinib, Encorafenib, and Cetuximab Combined to Treat BRAF-Mutant Colorectal Cancer) study demonstrated that a combination therapy consisting of BRAF, epidermal growth factor receptor, and mitogen-activated protein kinase kinase inhibitors could be a useful second-or third-line alternative. This review summarizes the current treatment strategies for *BRAF*-mutant mCRC.

Key Words: *BRAF* mutation; *V600* mutations; Metastatic colorectal cancer; Targeted therapies

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Core Tip: The treatment of *BRAF*-mutant metastatic colorectal cancer (mCRC) is particularly challenging. This review discusses the current treatment options for *BRAF*-mutant mCRC and the expanding role of targeted therapy in its management.

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INTRODUCTION

A relatively small proportion (10%-15%) of patients with metastatic colorectal cancer (mCRC) have activating mutations in the *BRAF* gene[1,2]. The majority of these mutations involve exon 15 of the gene that encodes the activation loop within the kinase domain of BRAF protein, resulting in the substitution of valine at amino acid position 600 of the BRAF protein by a different amino acid, such as glutamate (V600E), aspartate (V600D), or lysine (V600K)[3,4]. These substitutions, especially V600E, which accounts for more than 90% of *BRAF* mutations in mCRC, can lead to an abnormal increase in the catalytic activity of the BRAF protein by inducing conformational changes in its activation loop[5,6]. Consequently, contrary to their wild counterparts, which are ordinarily inactive in the cytoplasm in the absence of active *RAS* molecules, mutant BRAF proteins become persistently overactive monomers that can powerfully stimulate extracellular signal-regulated kinase (ERK) by directly phosphorylating and activating mitogen-activated protein kinase kinase (MEK) 1/2[7-9]. This condition leads to uncontrolled cell division and, consequently, cancer development.

Under normal conditions, however, the activation of *BRAF* and other members of the RAF family (ARAF and CRAF) is only initiated by the binding of active RAS-GTP to their RAS binding domain. First, a growth factor ligand (*i.e.*, epidermal growth factor) binds to its receptor [epidermal growth factor receptor (EGFR)] in the cell membrane, which leads to dimerization, autophosphorylation, and eventual activation of the receptor (Figure 1). The activated receptor recruits inactive RAS-GDP and converts it to active RAS-GTP[4-9]. The activated RAS binds to RAF and induces conformational changes in RAF, leading to RAF dimerization (*i.e.*, BRAF-CRAF), phosphorylation and kinase activation. The activated RAF phosphorylates and activates the MEK that, in turn, activates the ERK. The activated ERK translocates from the cytoplasm into the nucleus, where it regulates the activity of transcription factors that are vital for proper cell proliferation and differentiation. This RAS-RAF-MEK-ERK cascade is also known as mitogen-activated protein kinase (MAPK) signaling[4-9].

BRAF mutations initiate and drive the malignant transformation of colonic epithelial cells in the serrated pathway of colorectal tumorigenesis[10]. BRAF-mutant serrated colorectal cancer (CRC) mostly displays microsatellite instability (MSI), and extensive deoxyribonucleic acid (DNA) methylation[2,11]. DNA methylation at the CpG islands leads to epigenetic inactivation of the DNA mismatch repair protein MLH1, inducing an MSI phenotype. *BRAF*-mutant CRCs more commonly arise in the right colon and tend to be mucinous or poorly differentiated. They predominantly affect women and the elderly population. They have a distinct metastatic pattern preferentially involving the distant lymph nodes, and the peritoneum. Besides, they are less likely to metastasize to the lungs[12-18].

Patients with BRAF-mutant mCRC exhibit decreased sensitivity to chemotherapy, particularly in the second- and third-line settings[1,18,19]. A considerable proportion of them may not be able to receive second-line chemotherapy due to rapid progression and decline in performance status. Moreover, most patients who respond to the treatment do not benefit from surgical salvage interventions such as hepatic metastasectomy[20]. Consequently, these patients have a poorer prognosis than their counterparts with wild-type BRAF. A pooled analysis of four phase 3 studies (CAIRO, CAIRO2, COIN, and FOCUS) on mCRC showed that the median overall survival (OS) in patients with BRAF-mutant mCRC was shorter than that of patients with BRAF wild-type mCRC (11.4 *vs* 17.2 mo; $P < 0.001$)[21].

This aggressive chemorefractory nature of the disease creates significant challenges in the clinical management of patients with *BRAF*-mutant mCRC. However, emerging targeted therapies against BRAF and other regulatory elements of the MAPK pathway are still expanding the treatment options for these patients.

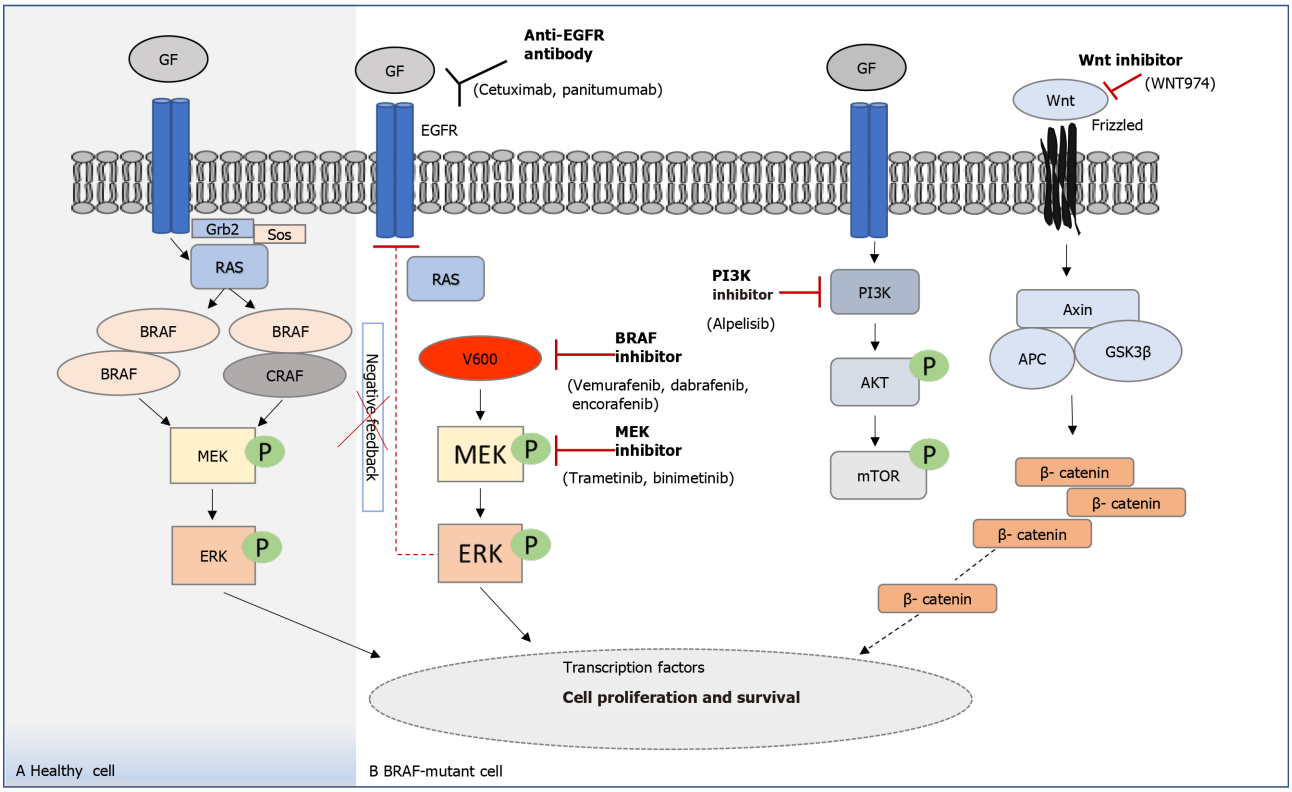

Figure 1 Activation of the mitogen-activated protein kinase (RAS-RAF-mitogen-activated protein kinase kinase-extracellular signal-regulated kinase) pathway due to *BRAF* V600 mutations and current targeted therapy options for metastatic colorectal cancer patients bearing these mutations. A: In healthy cells, a growth factor binds to and activates receptor tyrosine kinases on the cell membrane, inducing their dimerization. Then, the Grb2/Sos complex is recruited to the membrane to initiate RAS activation. Activated RAS triggers dimerization (*i.e.*, BRAF-BRAF or BRAF-CRAF) and activation of RAF proteins. RAF proteins activate the mitogen-activated protein kinase kinase-extracellular signal-regulated kinase (MEK-ERK) pathway to promote cell proliferation and survival; and B: In colorectal cancer cells bearing a *BRAF* V600 mutation, mutant BRAF proteins can signal as a monomer and potently activate the MEK-ERK pathway in a RAS independent manner, which accelerates tumor formation and progression. Drugs targeting BRAF (BRAF inhibitor) and MEK (MEK inhibitor) are currently used in the treatment of BRAF-mutant metastatic colorectal cancer (mCRC). The use of BRAF inhibitors suppresses the negative feedback from ERK to the epidermal growth factor receptor, resulting in the mitogen-activated protein kinase reactivation and the treatment resistance. Triplet inhibition of epidermal growth factor receptor, BRAF, and MEK is an emerging therapeutic approach for patients with BRAF-mutant mCRC. Crosstalk between the mitogen-activated protein kinase pathway and the PI3K and Wnt pathways can play a role in the survival of BRAF-mutant CRC cells and their resistance to BRAF inhibition. The PI3K and Wnt inhibitors may be part of the future treatment of *BRAF*-mutant mCRC.

CURRENT TREATMENT OPTIONS FOR *BRAF*-MUTANT mCRC

First-line treatment

Currently, classical irinotecan-and oxaliplatin-containing chemotherapy regimens appear to be the most appropriate initial management approach for patients with *BRAF*-mutant mCRC. In patients with adequate performance status, the use of a biological agent, preferably the anti-vascular endothelial growth factor antibody bevacizumab, along with chemotherapy, can be considered.

Recently, the use of more intensive chemotherapy regimens like FOLFOXIRI (5-fluorouracil, oxaliplatin, and irinotecan) has been recommended in this setting to overcome the resistance to chemotherapy in *BRAF*-mutant mCRC. In a phase 2 study conducted by Loupakis *et al*[22], the combination of FOLFOXIRI and bevacizumab was administered to 25 treatment-naïve patients with BRAF-mutant mCRC. This aggressive combination induced a high response rate (72%) with acceptable toxicity. The authors reported median progression-free survival (PFS) and OS periods of 11.8 and 24 mo, respectively.

More recently, the results of the TRIBE study were reported and indicated that FOLFOXIRI plus bevacizumab is very useful in the first-line treatment of patients with mCRC[23]. This phase 3 study compared FOLFOXIRI plus bevacizumab *vs* FOLFIRI plus bevacizumab in this setting and demonstrated the superiority of the FOLFOXIRI-containing arm over the FOLFIRI-containing arm in terms of response rate and survival. The authors found a trend toward survival benefit with FOLFOXIRI plus bevacizumab *vs* FOLFIRI plus bevacizumab for patients with *BRAF*-mutant tumors [*n* = 28; 19.0 *vs* 10.7 mo; hazard ratio (HR): 0.54], favoring the use of FOLFOXIRI plus

bevacizumab in *BRAF*-mutant mCRC.

Therefore, based on these results, the combination of FOLFOXIRI and bevacizumab can be proposed as a first-line therapy for carefully selected patients.

Many studies indicated that *BRAF* mutation might confer resistance to the anti-EGFR antibodies cetuximab and panitumumab by activating downstream effectors of the MAPK pathway independent of EGFR signaling. The results of these studies suggested that these agents should not be used in patients with *BRAF*-mutant mCRC. For example, a meta-analysis of 11 prospective studies found that among unselected mCRC patients treated with anti-EGFR antibody-containing therapies, patients with mutant BRAF had a lower response rate compared to those with wild-type BRAF (29% *vs* 33.5%, HR: 0.86; $P = 0.48$)[24]. However, a further analysis that included only patients with KRAS wild-type mCRC revealed an overall response rate (ORR) of 0.0% for patients with mutant BRAF and 36% for those with wild-type BRAF (HR: 0.14; $P = 0.004$). Subsequent studies confirmed these results[25-27].

A recent study conducted by the German AIO CRC study group (VOLFI trial) reported that first-line treatment with FOLFOXIRI plus panitumumab resulted in a significantly higher response rate compared to that obtained with FOLFOXIRI alone in patients with *BRAF*-mutant mCRC (71% *vs* 22%)[28]. This result suggests that such an aggressive upfront approach might be a reasonable option for these patients. However, it should be taken into consideration that the number of *BRAF*-mutant patients in the study was too small ($n = 16$). Besides, no significant differences in survival were noted between the two treatment arms. Therefore, there is a great need for more data to identify patients who are most likely to benefit from anti-EGFR antibody-based therapies in this setting.

An ongoing study is comparing FOLFOXIRI plus bevacizumab to FOLFOXIRI plus cetuximab as first-line treatment for *BRAF*-mutant mCRC (FIRE-4.5/AIO-KRK-0116). The results of this study might provide new insights into the first-line treatment of patients with *BRAF*-mutant mCRC.

Beyond first-line treatment

BRAF inhibition with selective BRAF inhibitors (vemurafenib, dabrafenib, and encorafenib) produced impressive results in the treatment of metastatic *BRAF*-mutant melanoma. Hence, these drugs were tested against *BRAF*-mutant mCRC. The initial clinical studies demonstrated that only a small proportion (approximately 5%) of the *BRAF*-mutant mCRC patients were sensitive to BRAF inhibition[28-32]. This outcome was highly discordant with preclinical observations indicating that BRAF inhibition can efficiently inhibit the proliferation of *BRAF*-mutant CRC cells and induce tumor regression *in vivo* and *in vitro*[33].

Considerable preclinical research efforts have been made to identify molecular mechanisms underlying resistance to BRAF inhibitor therapy in *BRAF*-mutant CRC. The obtained data showed that the administration of a BRAF inhibitor initially causes a rapid decline in the magnitude of MAPK activity in tumor cells, leading to the loss of the negative feedback between ERK and EGFR. This event enhances EGFR-mediated RAS activity, leading to RAF heterodimer (*i.e.*, BRAF-CRAF) formation and C-RAF transactivation, resulting in a rebound activation of the MAPK pathway[34-36].

Overactivation of the PI3K pathway was found in *BRAF*-mutant CRC cells mediating *de novo* resistance to BRAF inhibitors[33,37,38]. Besides, CRC cell lines with activating PIK3CA mutations or loss of PTEN expression were found to be more resistant to the growth-inhibiting effects of BRAF inhibitors compared to cell lines without these alterations[3,37].

Preclinical studies also support the role of Wnt signaling in the development of resistance to BRAF inhibition in *BRAF*-mutant CRC[39]. Treatment with BRAF inhibitors was found to induce focal adhesion kinase-dependent Wnt/β-catenin pathway activation in the *BRAF* V600E-mutant CRC cell lines[39]. Activation of the Wnt/β-catenin pathway promoted BRAF inhibitor resistance independent of MAPK pathway reactivation. The mechanisms underlying this resistance are unknown. It was postulated that the activated Wnt pathway might contribute to BRAF inhibitor resistance by enhancing the stemness properties of CRC cells[39].

Overall, these data suggest that a combinatorial approach targeting the critical downstream components of MAPK signaling and other relevant pathways might be more effective in the treatment of *BRAF*-mutant mCRC.

Dual inhibition of BRAF and EGFR

A pilot trial investigated the efficacy and safety of a combination of vemurafenib and panitumumab in 15 patients with *BRAF* mutant-mCRC who had previously received at least one line of chemotherapy[40]. Two patients (13%) had a confirmed partial

response, and two patients had stable disease lasting at least six months (Table 1). Low-grade acneiform skin rash and grade 3-4 increase in ALT, AST, and alkaline phosphatase were the most common side effects. Although this dual-targeted therapy failed to produce a satisfactory outcome, it seemed to work better than BRAF inhibitor monotherapy.

A phase 2 randomized study designed by Southwest Oncology Group (SWOG 1406) evaluated the efficacy of irinotecan and cetuximab with and without vemurafenib in patients with refractory *BRAF* V600-mutant mCRC[41]. In murine models of *BRAF*-mutant mCRC, the combination of irinotecan, cetuximab, and vemurafenib showed higher antitumor activity than irinotecan and cetuximab or vemurafenib and cetuximab[33]. Additionally, a phase 1 study demonstrated that this combination was safe and appeared more effective than vemurafenib alone and irinotecan plus cetuximab, suggesting that this triplet regimen deserved further evaluation as a potential treatment for *BRAF*-mutant mCRC[42]. Thus, these preliminary findings prompted the SWOG 1406 trial. The study confirmed earlier findings and showed that the addition of vemurafenib to the combination of cetuximab and irinotecan led to a prolonged PFS (4.4 *vs* 2.2 mo; HR 0.42; $P < 0.001$) and a higher disease control rate (67% *vs* 22%; $P < 0.001$), indicating that simultaneous inhibition of BRAF and EGFR is an effective strategy for treating *BRAF*-mutant mCRC.

Dual inhibition of BRAF and MEK

Preclinical studies performed in *BRAF*-mutant CRC cell lines showed a robust antitumor synergy between BRAF and MEK inhibitors[43]. On the basis of these data, Corcoran *et al*[44] assessed the efficacy of dabrafenib plus the MEK inhibitor trametinib in 43 heavily pretreated patients with *BRAF*-mutant mCRC. One complete and four partial responses were obtained, and the ORR was 12%. Despite this relatively promising response rate, the median PFS was 3.5 mo. The authors also investigated the pharmacodynamic effects of the treatment in paired tumor biopsies taken from baseline and after 15 d of treatment. They observed that the combination of dabrafenib plus trametinib was not enough to inhibit MAPK activity effectively in *BRAF*-mutant CRC cells, which was probably the most critical factor limiting its efficacy.

Triplet therapies

Combined BRAF, EGFR, and MEK inhibition: Corcoran *et al*[36] hypothesized that a combined inhibition strategy targeting the BRAF, MEK, and EGFR pathways may lead to improved efficacy in *BRAF*-mutant mCRC by providing more profound inhibition of the MAPK pathway. They conducted a 3-arm randomized controlled study to compare dabrafenib and panitumumab (D + P), dabrafenib, trametinib, and panitumumab (D + T + P), and trametinib and panitumumab (T + P) in pretreated *BRAF*-mutant mCRC[36]. The ORRs in these treatment arms were 10%, 21%, and 0%, respectively; the median PFS periods were 3.5, 4.2, and 2.6 mo, respectively; and the median OS periods were 13.2, 9.1, and 8.2 mo, respectively. The combined frequency of the most common adverse events (diarrhea, acneiform rash, nausea, fatigue, and pyrexia) was higher in the D + T + P arm than in the D + P arm. Eighteen percent of patients receiving D + T + P discontinued treatment due to an adverse event. Pharmacodynamic studies demonstrated that both D + T + P and D + P significantly decreased the levels of phosphorylated ERK in paired on-treatment biopsy specimens of the patients, but T + P did not. However, the degree of ERK inhibition produced by D + T + P and D + P remained lower than those obtained by BRAF inhibitor monotherapies in melanoma samples, possibly explaining why the efficacy of these treatment approaches in CRC still falls short of BRAF inhibitors monotherapy in melanoma.

More recently, the results of the first interim analyses of the BEACON study were reported[45]. This phase 3 study compared encorafenib (a novel BRAF inhibitor with improved pharmacological properties) plus the MEK inhibitor binimetinib plus cetuximab (triplet-therapy) *vs* encorafenib plus cetuximab (doublet-therapy) *vs* the investigators' choice of either irinotecan or FOLFIRI plus cetuximab (control therapy) in patients with *BRAF*-mutant mCRC in the second-or third-line setting. The primary endpoints were OS and ORR in the triplet-therapy arm in comparison with those in the control therapy arm. The interim analysis showed a median OS of 9.0 mo with the triplet-therapy and 5.4 mo with the control therapy (HR: 0.52; 95%CI: 0.39-0.70; $P < 0.001$). The ORR was 26% for patients receiving triplet therapy, [which was higher (34%) in a patient subgroup that received just one prior therapy line], and 2% for those receiving control therapy ($P < 0.001$). The median OS in the doublet-therapy arm was 8.4 mo (HR *vs* control therapy, 0.60; 95%CI: 0.45-0.79; $P < 0.001$). Grade 3 or higher adverse events, including diarrhea, nausea, vomiting, and acneiform dermatitis, were

Table 1 Summary of selecting trials investigating the efficacy of targeted therapies in *BRAF*-mutant mutant metastatic colorectal cancer

Ref.	Design	Treatment arm(s)	Summary of results
Kopetz *et al*[30]	Phase 2	Vemurafenib (n = 21)	One (5%) patient had a partial response, 7 had stable disease. Median PFS was 2.1 mo
Yaeger *et al*[40]	Phase 2	Vemurafenib + Panitumumab (n = 15)	Two patients had partial responses; six achieved tumor shrinkage. Median PFS was 3.2 mo; median OS was 7.6 mo
Corcoran *et al*[44]	Phase 2	Dabrafenib + Trametinib (n = 43)	One patient had a complete response; five patients had a partial response, with an ORR of 12%; 56% of patients had stable disease
Corcoran *et al*[36]	Phase 1/2	Dabrafenib + Panitumumab (D + P) (n = 20) *vs* Dabrafenib + Trametinib + Panitumumab (D + T + P) (n=91) *vs* Trametinib + Panitumumab (T + P) (n = 31)	The ORR was 10%, 21%, and 0% for the D + P, D + T + P, and T + P, respectively. The median PFS was 3.5 mo in the D + P arm, 4.2 mo in the D + T + P arm, and 2.6 mo in the T + P arm
Kopetz *et al*[41], (SWOG 1406 trial)	Phase 2	Irinotecan + Cetuximab + Vemurafenib (n = 54) *vs* Irinotecan + Cetuximab (n = 52)	The median PFS 4.4 *vs* 2.0 mo (P < 0.001); the ORR 16% *vs* 4% (P = 0.09); disease control rate 67% *vs* 22% (P < 0.001)
van Geel *et al*[47]	Phase 2	Encorafenib + Cetuximab (n = 50) *vs* Encorafenib + Cetuximab + Alpelisib (n = 52)	The median PFS was 4.2 mo for encorafenib + cetuximab, and 5.4 mo for triplet therapy. The ORR rate was 22% and 27%, respectively
Kopetz *et al*[45], (BEACON CRC trial)	Phase 3	Encorafenib + Cetuximab + Binimetinib (Triplet arm) (n = 224) *vs* Encorafenib + Cetuximab (Doublet arm) (n = 220) *vs* Irinotecan/FOLFIRI + Cetuximab (Control arm) (n = 221)	The median OS was 9.0 mo in the triplet arm (HR for death *vs* control arm, 0.52; 95%CI: 0.39-0.70; P < 0.001), 8.4 mo in the doublet arm (HR for death *vs* control arm, 0.60; 95%CI: 0.45-0.79; P < 0.001), and 5.4 mo in the control arm. The ORR was 26%, 20%, and 2% for the triplet arm, the doublet arm, and the control arm, respectively

mCRC: Metastatic colorectal cancer; PFS: Progression-free survival; OS: Overall survival; ORR: Overall response rate; HR: Hazard ratio.

noted in 58%, 50%, and 61% of patients receiving triplet therapy, doublet therapy, and control therapy, respectively.

Update survival analysis from the BEACON study providing an additional six months of follow-up indicated that the median OS was 9.3 mo (95%CI: 8.2-10.8) with the triplet therapy, 9.3 mo (95%CI: 8.0-11.3) with the doublet therapy, and 5.9 mo (95%CI: 5.1-7.1) with the control therapy. The ORRs were 27%, 20%, and 2%, respectively[46]. These results suggested that the use of binimetinib, together with encorafenib plus cetuximab, may not provide additional survival benefit for these patients.

In April 2020, the United States Food and Drug Administration approved the combination of encorafenib and cetuximab for the treatment of patients with *BRAF* V600E-mutant mCRC who progressed despite 1 or 2 prior lines of therapy.

Combined BRAF, EGFR, and PI3K inhibition

Triple inhibition of BRAF, EGFR, and PI3K showed promising antitumor activity in preclinical models of *BRAF*-mutant mCRC[35,37], which led to the initiation of a phase 1b/2 study investigating the efficacy of encorafenib plus cetuximab with or without the PI3K-α-specific subunit inhibitor alpelisib in pretreated patients with BRAF-mutant mCRC[47]. In the phase Ib portion, a total of 54 patients received either encorafenib plus cetuximab (n = 26) or encorafenib plus cetuximab plus alpelisib (n =

28). The ORR was 19% in patients receiving dual combination treatment and 18% in those receiving triple combination treatment. Both combination treatments demonstrated acceptable safety profiles. In the phase 2 portion of the study, a total of 102 patients with *BRAF*-mutant mCRC who failed one or more therapeutic regimens were randomized to a doublet (encorafenib plus cetuximab) or triplet (encorafenib plus cetuximab plus alpelisib) therapy arm[48]. The primary endpoint was PFS. The interim analysis showed improvement in PFS with the addition of alpelisib (5.4 *vs* 4.2 mo; HR: 0.69). The ORR was 27% in the triplet therapy arm *vs* 22% in the doublet therapy arm. Grade ≥ 3 toxicities were reported in 58% of the patients in the doublet therapy arm and 79% of those in the triplet therapy arm.

Combined BRAF, EGFR, and Wnt inhibition

A phase 1/2 study (NCT02278133) is currently investigating the safety and efficacy of a combination of the Wnt inhibitor WNT974, the BRAF inhibitor LGX818, and cetuximab in refractory mCRC patients harboring both *BRAF*-V600 and Wnt pathway mutations. The study completed enrollment of 20 patients in 2017. The preliminary results are still expected.

CONCLUSION

Despite some recent progress, the management of *BRAF*-mutant mCRC remains a significant challenge. In newly diagnosed BRAF-mutant mCRC patients with good performance status, FOLFOXIRI plus bevacizumab can be considered a first-choice treatment. However, elderly patients (age > 70 years) and patients with impaired performance status may be appropriate candidates for non-intensive chemotherapy (fluoropyrimidine alone or in combination with oxaliplatin or irinotecan) with or without bevacizumab. We do not know yet whether BRAF-directed therapies may be an effective first-line option for at least some cases. An ongoing phase 2 study, ANCHOR-CRC, which is testing the combination of encorafenib, binimetinib, and cetuximab or any other anti-epidermal growth factor receptor inhibitor in previously untreated patients with *BRAF* V600E-mutant mCRC, might clarify their role in this setting[49].

Patients failing first-line treatment are candidates for targeted therapies. In these patients, encorafenib plus cetuximab with or without binimetinib currently seems to be the most appropriate treatment option. In selected cases, however, the combination of irinotecan, cetuximab, and vemurafenib can be administered.

On the other hand, since the current treatment options have relatively limited therapeutic success, there is a substantial need for additional treatment modalities. The Phase II Checkmate-142 study showed that immunotherapy with nivolumab, an anti-programmed death-1 monoclonal antibody, may provide durable disease control and long-term survival in pretreated patients with MSI-high (MSI-H) mCRC[50]. In this study, an ORR of 25% was observed in a subgroup of patients with BRAF-mutant tumors. A subsequent report suggested that the combination of nivolumab and low-dose ipilimumab, a monoclonal antibody targeting the cytotoxic T-lymphocyte antigen 4 immune checkpoint receptor, might be more effective than nivolumab alone in this setting[51]. These results implicated that immunotherapy might be an option, especially in the salvage setting, for a subset of patients with MSI-H BRAF-mutant mCRC. Additionally, several ongoing clinical trials are evaluating combinations of immunotherapies and targeted therapies in previously treated and untreated patients with BRAF-mutant/microsatellite-stable mCRC, such as NCT03668431 (dabrafenib + trametinib + spartalizumab), NCT04017650 (encorafenib + cetuximab + nivolumab, and NCT04044430 (encorafenib + binimetinib + nivolumab).

Preclinical studies showed that ERK inhibition could overcome the acquired resistance to BRAF and MEK inhibition in *BRAF*-mutant CRC cell lines, leading to enhanced inhibition of cell growth[52,53]. In early-phase clinical trials, the ERK inhibitor ulixertinib demonstrated encouraging signs of antitumor activity against various solid tumors harboring *BRAF* mutations, including mCRC[54]. In these studies, ulixertinib was found to be effective in patients who were either naïve or resistant to BRAF and/or MEK inhibitors[54]. These findings suggested that the use of ERK inhibitors, either alone or in combination with BRAF and epidermal growth factor receptor inhibitors, could be a component of future therapeutic strategies for *BRAF*-mutant mCRC.

In conclusion, the introduction of triplet targeted therapy into clinical practice has significantly expanded the treatment options for *BRAF*-mutant mCRC. However, more

efforts are needed to identify novel approaches to overcome treatment resistance in this aggressive malignancy.

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