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REVIEW

Management of *BRAF*-mutant metastatic colorectal cancer: a review of treatment options and evidence-based guidelines

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Available online 7 April 2021

Background: Colorectal cancer (CRC) is still a leading cause of cancer-related deaths in the United States and worldwide, despite recent improvements in cancer management. CRC, like many malignancies, is a heterogeneous disease, with subtypes characterized by genetic alterations. One common mutation in CRC is in the *BRAF* gene (most commonly V600E substitution). This occurs in ∼10% of patients with metastatic CRC (mCRC) and is a marker of poor prognosis.
Design: Herein, we review the clinical and translational literature on the role of the *BRAF* V600E mutation in the pathogenesis of mCRC, its mechanisms as a prognostic marker, and its potential utility as a predictive marker of treatment response. We then summarize the current evidence-based recommendations for management of *BRAF* V600E-mutated mCRC, with a focus on recent clinical research advances in this setting.
Results: The current standard therapies for first-line treatment of *BRAF*-mutated mCRC are chemotherapy with bevacizumab as well as 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab in patients with a good performance status. Combination strategies involving mitogen-activated protein kinase (MAPK) pathway blockade have shown promising results for the treatment of patients with *BRAF* V600E-mutated mCRC. The Binimetinib, Encorafenib, And Cetuximab cOmbiNed to treat BRAF-mutant ColoRectal Cancer (BEACON CRC) study represents the largest study in this population to date and has given strong clinical evidence to support BRAF and epidermal growth factor receptor inhibition with the combination of encorafenib plus cetuximab.
Conclusions: The treatment of *BRAF*-mutated mCRC has evolved rapidly over the last several years. Recently, combination strategies involving MAPK pathway blockade have shown promising results in *BRAF* V600E-mutated mCRC, and other potential targets continue to be explored. In addition, a greater understanding of the role of *BRAF* V600E mutation in the pathogenesis of CRC should also continue to fuel advances in the management of patients with mCRC harboring this genetic aberration.
Key words: metastatic colorectal cancer, *BRAF* mutation, pathophysiology, prognostic markers, management

INTRODUCTION

Despite recent improvements in cancer research, colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States, with ∼147 950 new cases and 53 200 deaths per year.[1,2] Worldwide, CRC is the second highest cause of cancer-related mortality as well as the third most common cancer.[3]

For patients diagnosed with CRC at an early stage of the disease, surgery is the primary treatment modality and can be curative. However, a large number of patients are diagnosed at an advanced/metastatic stage of the disease, with a 5-year survival rate of roughly 14%.[2] For these patients, treatment has been based largely on chemotherapy. Common agents include irinotecan- or oxaliplatin-based combinations such as 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI); 5-FU, leucovorin, and oxaliplatin (FOLFOX); 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI); capecitabine and irinotecan (CAPIRI); or capecitabine and oxaliplatin (CAPOX) regimens.[4] These therapies have demonstrated a median survival of ∼17-23 months.[5-7] Improvements in overall survival (OS) for patients with metastatic CRC (mCRC) have more recently been observed with targeted therapies, such as antibodies against the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).[8-15]

CRC, like many malignancies, is a heterogeneous disease, with subtypes characterized by genetic alterations. For

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example, mutations in the *BRAF* gene occur in ~12% of patients with mCRC, with recent estimates ranging from as low as 5% to as high as 21%.[16-22] A majority of these mutations resulted in a V600E substitution.[23] These mutations are associated with the female sex, are often right-sided and advanced stage, are of a mucinous histology, have defective mismatch repair, and have a serrated adenoma pathway.[22,24,25] Patients with *BRAF* V600E-mutated CRC have a median OS of ~11 months, highlighting their poor prognosis, as well as a lack of response to standard therapies.[24,25] Of note, non-V600E *BRAF* mutations occur in ~2.2% of all patients with mCRC and mostly define a clinically distinct subtype of CRC with a good prognosis.[25] Although there are no current treatment recommendations for non-V600E *BRAF*-mutated CRC, patients with this subtype have a similar prognosis as those with wild-type *RAS*/*BRAF* (*RAS* WT/*BRAF* WT).[26] Several case reports suggest that anti-EGFR therapy may benefit patients with non-V600 *BRAF*-mutated CRC.[26,27]

ROLE OF *BRAF* MUTATIONS IN CRC PATHOPHYSIOLOGY

Mutations in the *BRAF* gene in CRC pathogenesis develop within the serrated pathway (Figure 1A). Tumors with *BRAF* V600E mutations are often associated with a high mutational burden, microsatellite instability (MSI), and a CpG island methylator phenotype (CIMP), with high levels of epigenetic modulation of gene expression through DNA methylation.[22,28-30] *BRAF*-mutant tumors have been found to be 70% CIMP-high[31] and were more frequently found in MSI-high (MSI-H) tumors (~30%-50%) relative to microsatellite-stable (MSS) tumors.[29,32] Recently, four distinct subgroups in CRC [i.e. the consensus of molecular subtypes (CMS)] were identified based on intrinsic gene expression profile patterns.[33] The majority of *BRAF*-mutant CRCs are CMS subtype 1 (MSI immune), which are associated with deficient DNA repair, hypermethylation, and high mutational burden.[33] This is consistent with the findings from The Cancer Genome Atlas project.

Two subtypes of *BRAF*-mutant CRC classification, BM1 and BM2, have also been reported based on differential gene expression with distinct molecular patterns.[21] BM1 is characterized by *KRAS/AKT* pathway activation, mechanistic target of rapamycin kinase/eukaryotic translation initiation factor 4E-binding protein 1 deregulation, and epithelial—mesenchymal transition-related processes with *KRAS* signaling and immune response, whereas BM2 is

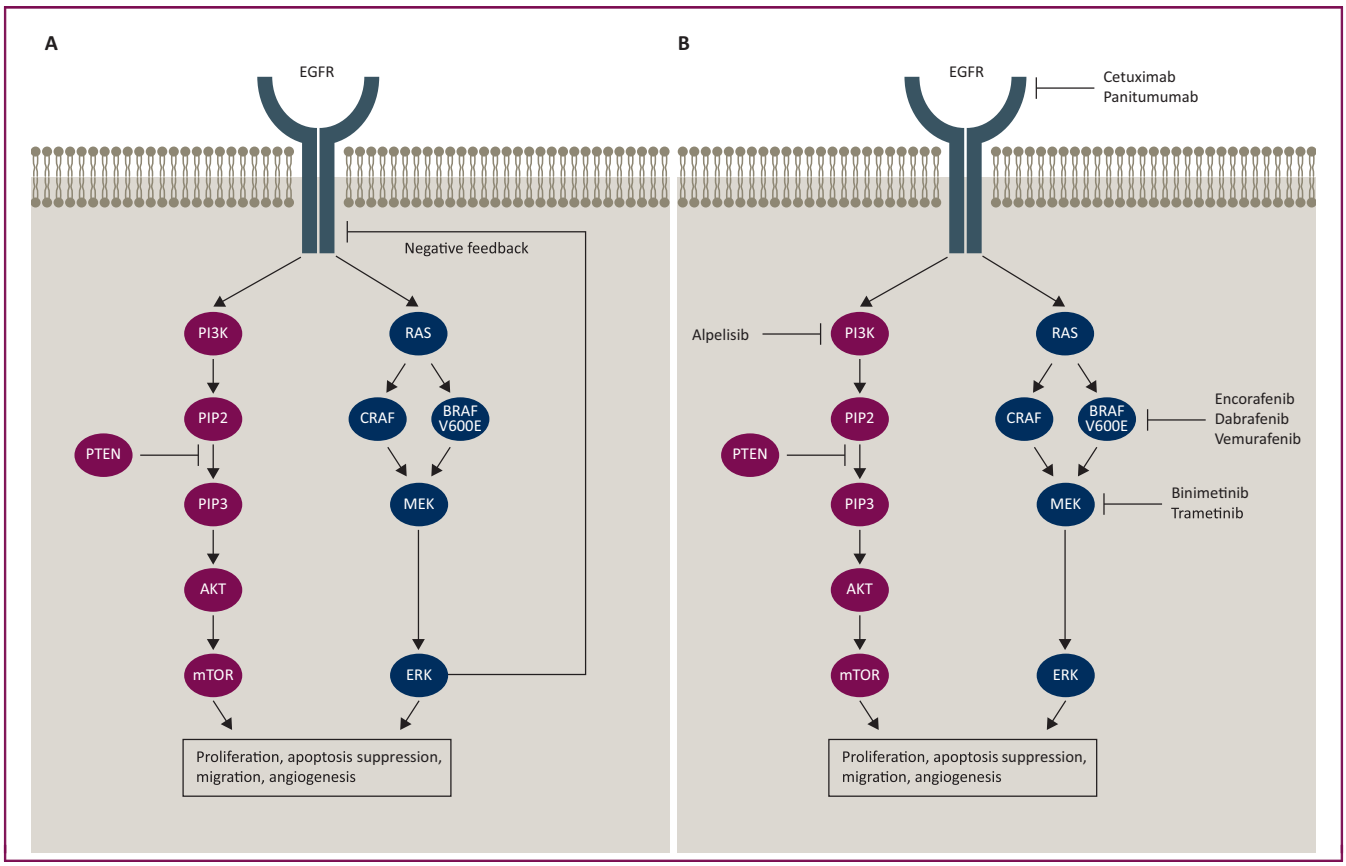

Figure 1. (A) The RAS/BRAF/MEK/ERK and the PI3K/AKT/mTOR pathways and (B) their inhibitors.
(A) In the absence of inhibitors, BRAF protein with a V600E mutation activates MEK and ERK resulting in cell proliferation, suppression of apoptosis, cell migration, and angiogenesis. ERK activation suppresses EGFR-mediated RAS activation through negative feedback on EGFR. (B) Monotherapy with a BRAF inhibitor (encorafenib, dabrafenib, vemurafenib) blocks the activity of mutated BRAF, subsequently removing the negative feedback on EGFR and resulting in paradoxical activation of the MAPK pathway. Adding an EGFR inhibitor (cetuximab, panitumumab) prevents this paradoxical activation. Addition of a MEK inhibitor (binimetinib, trametinib) or PI3K inhibitor (alpelisib) further suppresses MAPK signaling.
EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog.

characterized by dysregulation of the cell cycle and cycle checkpoint-related processes.[21,34] This two-subtype classification of *BRAF*-mutant CRC may help explain differences in response to treatment and may be useful for predicting individual patient prognosis, with patients belonging to the BM1 subtype exhibiting a worse outcome.[21,34]

BRAF MUTATIONS AS PROGNOSTIC FACTORS

The prognostic value of *BRAF* V600E mutations in CRC has been demonstrated in several clinical studies, which showed *BRAF* mutations associated with poor survival relative to patients with *BRAF* WT CRC.[35-42] Median survival can be approximately twofold to threefold longer in patients with WT tumors relative to *BRAF*-mutant mCRC (i.e. 2-3 years versus 1 year, respectively).[13,14,35,40,41,43] These findings are largely consistent with prospective mutational analyses from randomized controlled studies as well as retrospective studies in the literature that have found *BRAF* mutations to be a prognostic biomarker.[24,41,42]

The poor prognosis of *BRAF*-mutant mCRC may be due, in part, to aberrant programmed cell death.[44,45] *BRAF* V600E mutations have been shown to suppress expression of caudal type homeobox 2 (CDX2), a tumor suppressor and transcription factor involved in the regulation of intestinal epithelial cell differentiation, cell adhesion, and polarity. Metastases and poor prognosis in CRC have been associated with the loss of CDX2.[46] Given their overall favorable prognosis, MSI-H tumors may attenuate the adverse prognostic impact of *BRAF* mutations, in particular in earlier-stage disease.[47,48] *BRAF*-mutated MSI-H tumors have a less aggressive clinical phenotype and improved OS relative to *BRAF*-mutant MSS tumors.[24,41]

Several studies have proposed that the *BRAF* V600E mutation is a predictive marker for limited sensitivity to EGFR monoclonal antibodies (e.g. cetuximab, panitumumab) alone or when combined with chemotherapy.[36] Based on these findings, exploration of relevant therapeutic strategies targeting the unique tumor biology of the *BRAF*-mutant CRC population is warranted.

TREATMENT OF *BRAF*-MUTANT CRC

There are a number of therapeutic options available for patients with *BRAF*-mutated mCRC (Figure 1B). Systemic chemotherapy has been the foundation of therapy for the past several decades. For example, the National Comprehensive Cancer Network (NCCN) guidelines note that combination chemotherapy provides survival benefit and remains the agreed standard of care in patients with appropriate performance status.[49] First-line chemotherapy options include FOLFOX, FOLFIRI, and capecitabine plus oxaliplatin.[49] The TRIplet plus BEvacizumab (TRIBE) study evaluated FOLFIRI plus bevacizumab versus FOLFOXIRI plus bevacizumab as initial therapy in 508 patients with mCRC.[50] A total of 28 patients with *BRAF* V600E mutations were enrolled (12 patients in the FOLFIRI arm, 16 patients in the FOLFOXIRI arm). The median OS was 37.1 months in the *RAS* and *BRAF* WT subgroup and 13.4 months in the *BRAF* mutation subgroup [hazard ratio (HR) 2.79; 95% confidence interval (CI) 1.75-4.46; $P < 0.0001$].[13] The median OS of patients with *BRAF* V600E mutations treated with FOLFOXIRI plus bevacizumab in the TRIBE study was 19.0 months compared with 10.7 months in the FOLFIRI plus bevacizumab arm (HR 0.54; 95% CI 0.24-1.20). Based on an analysis of treatment effect and *BRAF* mutation status, patients with *BRAF* V600E mutations appeared to derive equivalent benefit as their *BRAF* WT counterparts from FOLFOXIRI versus FOLFIRI. However, these findings were not confirmed on the follow-up phase III TRIBE-2 trial, during which patients were randomized to FOLFOXIRI plus bevacizumab or to FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab.[51] In addition, a recent meta-analysis of five randomized trials comparing FOLFOXIRI plus bevacizumab to a doublet combination plus bevacizumab failed to show on subgroup analysis any advantage to FOLFOXIRI plus bevacizumab.[52] We conclude that there is insufficient evidence of a clear benefit to a triplet cytotoxic regimen over doublet chemotherapy in the front-line treatment of *BRAF* V600E-mutated mCRC.

Targeted therapies are also recommended in several guidelines for some patients with *BRAF*-mutant CRC. Patients with *BRAF*-mutated tumors appear to benefit from anti-VEGF therapy, similar to patients with *BRAF* WT tumors, as shown in a retrospective analysis of the pivotal mCRC phase III study and a *post hoc* analysis of the phase III Australian Gastrointestinal Trials Group Mitomycin, Avastin, Xeloda (AGITG MAX) trial.[28,34,37,53] Other VEGF inhibitors, such as ramucirumab and ziv-aflibercept, would presumably have potential therapeutic benefit based on similar mechanism of action, but have limited evidence in patients with *BRAF*-mutant CRC.[54,55]

The EGFR monoclonal antibodies cetuximab and panitumumab are United States Food and Drug Administration (FDA)-approved for use in patients with *KRAS* and *NRAS* (*RAS*) WT mCRC.[56,57] *BRAF* V600E-mutated CRC tumors are postulated to be resistant to EGFR inhibition based on activation of the mitogen-activated protein kinase (MAPK) pathway by *BRAF* mutations downstream of EGFR.[28] There is currently limited evidence that the addition of anti-EGFR therapy to chemotherapy results in a clinically significant benefit in *BRAF*-mutated mCRC.[14,38,40,42] A retrospective analysis of prospectively conducted trials did not show a significant additive benefit from anti-EGFR therapy.[58] In addition, the combination of cetuximab and irinotecan, with or without vemurafenib, was associated with modest outcomes in second- and third-line treatment of metastatic *BRAF* V600E-mutated mCRC.[59] In the refractory setting, EGFR-targeted therapies do not have high single-agent activity in patients with *BRAF*-mutated mCRC and thus are not likely to provide a benefit to these patients, based on data from a small number of patients.[36,60-62]

BRAF inhibitors as single agents have only shown modest activity as monotherapy in *BRAF*-mutated mCRC, with response rates of ~5% (Table 1).[62,63] Preclinically, *BRAF*-mutant CRC cells have decreased sensitivity to *BRAF*

Table 1. Clinical trials with BRAF inhibitors in *BRAF*-mutated mCRC

	Treatment	Patients, n	RR (%)	mPFS (months)	mOS (months)
BRAF inhibitor monotherapy or with MEK inhibitor					
BRAF + MEK inhibitor	Vemurafenib[63]	21	5	2.1	7.7
	Vemurafenib[64]	10	0	4.5	9.3
	Encorafenib[65]	18	0	4	—
	Dabrafenib + trametinib[66]	43	12	3.5	—
BRAF inhibitor plus anti-EGFR antibody					
BRAF + EGFR inhibitor	Vemurafenib + cetuximab[64]	27	3.7	3.7	7.1
	Vemurafenib + panitumumab[67]	15	13	3.2	7.6
	Dabrafenib + panitumumab[68]	20	10	3.5	—
	Encorafenib + cetuximab[69]	50	22	4.2	—
	Encorafenib + cetuximab[70]	220	20	4.2	8.4
BRAF inhibitor and anti-EGFR antibody with MEK or PI3K inhibitors					
BRAF + MEK + EGFR inhibitors	Dabrafenib + trametinib + panitumumab[68]	91	21	4.2	9.1
	Encorafenib + cetuximab + binimetinib[70]	224	26	4.3	9.0
BRAF + EGFR + PI3K inhibitors	Encorafenib + cetuximab + alpelisib[69]	52	27	5.4	15.2
BRAF inhibitor and anti-EGFR antibody and chemotherapy					
BRAF + EGFR inhibitors + irinotecan	Vemurafenib + cetuximab + irinotecan[59]	106	16	4.4	—

EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; mOS, median overall survival; mPFS, median progression-free survival; PI3K, phosphoinositide 3-kinase; RR, response rate.

inhibitors relative to melanoma cells, with transient suppression of phosphorylated ERK followed by rapid EGFR-mediated reactivation of *RAS* and *C-RAF*.[71] The activity of *BRAF* inhibitors may be circumvented by the reactivation of EGFR, explaining in part the modest efficacy relative to melanoma cells, which express low levels of EGFR.[72] BRAF and EGFR inhibitor combinations resulted in synergistic inhibition of tumor growth in *BRAF* V600E-mutant CRC xenograft models.[71,72] Subsequent clinical studies of EGFR-targeted monoclonal antibodies combined with BRAF inhibition suggested improved activity compared with that of single-agent BRAF inhibitors (Table 1).[62,64,67-70]

Acquired oncogene mutations (i.e. *KRAS*, *NRAS*, and *MAPK* 1) and copy number amplifications in *BRAF* are observed in analyses of resistance mechanisms to *BRAF*-targeted therapies and may help explain the loss[73,74] of response.[71] Additional targeted agents against effectors in this pathway could result in deeper antitumor responses and provide a rationale for dual inhibition of multiple targets to attempt to improve outcomes for patients with *BRAF* V600E-mutated mCRC.

To test the therapeutic utility of these findings, several clinical trials have been conducted with combinations of agents, with the goal of overcoming resistance to BRAF inhibitor monotherapy. For example, the combination of vemurafenib and cetuximab was evaluated in 27 patients with *BRAF* V600E-mutated mCRC. One patient had a partial response and 69% had stable disease with a median OS and progression-free survival (PFS) of 7.1 and 3.7 months, respectively.[64] The combination of vemurafenib and panitumumab was also investigated in 15 pre-treated patients with *BRAF* V600E-mutated mCRC. Results from this trial included two patients with partial response and six with stable disease.[67] Additional treatments involving other combinations of BRAF and EGFR inhibitors have also been explored clinically with response rates ranging from 10% to 39%.[69,75,76] The combination of BRAF and MEK inhibitors has been evaluated in patients with *BRAF*-mutated mCRC, resulting in a modest overall response rate (ORR) of 12% and a median PFS of 3.5 months (95% CI 3.4-4.0 months in a study of 43 patients treated with dabrafenib and trametinib).[62]

The doublet combination of the BRAF inhibitor encorafenib and the EGFR monoclonal antibody cetuximab showed promising activity in early clinical trials.[69,77] The addition of an MEK inhibitor to BRAF inhibition has also been found to increase inhibition of the MAPK pathway and produce potentially greater antitumor activity in preclinical and initial clinical studies.[68,78]

Triplet combinations have been evaluated in an attempt to improve outcomes for patients with *BRAF*-mutant mCRC. The combinations of dabrafenib plus panitumumab, dabrafenib and trametinib plus panitumumab, and trametinib plus panitumumab were explored in a recent trial, which resulted in an improved ORR for the triplet therapy, but with an increase in certain adverse events such as grade 3/4 diarrhea relative to the doublet regimens.[68] Combination with phosphoinositide 3-kinase (PI3K) inhibitors has also been explored. In a phase Ib dose-escalation study, the combinations of encorafenib and cetuximab versus encorafenib, cetuximab, and the PI3K inhibitor alpelisib were evaluated in 28 patients with refractory *BRAF*-mutated CRC. An ORR of 18% and a disease control rate of 93% were reported for the triplet regimen of encorafenib, cetuximab, and alpelisib.[77] In a subsequent phase II study in 52 patients treated with these regimens, PFS was numerically higher for the triplet versus the doublet regimen (5.4 versus 4.2 months), with higher frequency of adverse events with the triplet, including anemia, hyperglycemia, and increased lipase.[69] Additional combinations, such as vemurafenib, cetuximab, and irinotecan, as well as irinotecan and cetuximab, with or without vemurafenib, have been tested with modest efficacy results.[59,79]

Recently, the initial results of the phase III BEACON trial were published, in which 665 patients with *BRAF*

V600E-mutated mCRC who had had disease progression after one or two previous treatment regimens were randomized 1 : 1 : 1 to receive encorafenib, cetuximab, and binimetinib (a MEK inhibitor) versus encorafenib and cetuximab versus irinotecan plus FOLFIRI and cetuximab.[70,80-82] More than 90% of patients received prior oxaliplatin and ∼52% of patients received prior irinotecan before enrollment into this study. This trial represents the largest cohort ever studied for this population and the first phase III trial to demonstrate a survival and response advantage in the setting of pre-treated *BRAF*-mutated CRC. In the BEACON CRC study, eligible patients were stratified by the Eastern Cooperative Oncology Group performance status, prior use of irinotecan, and cetuximab formulation (US-licensed versus European-approved). Primary endpoints for the BEACON CRC study were OS and independently reviewed confirmed ORR for the triplet combination compared with the control. A key secondary endpoint was OS for the encorafenib plus cetuximab regimen versus control. Other secondary endpoints included OS for the doublet arm compared with the control arm as well as PFS, duration of response, and safety.

In the most recent analysis of the BEACON CRC study, the encorafenib plus cetuximab regimen significantly improved OS relative to the control group, with a median OS of 9.3 months (95% CI 8.0-11.3 months) compared with 5.9 months (95% CI 5.1-7.1 months) for the control regimens (HR 0.61; 95% CI 0.48-0.77). The OS results were consistent across a broad range of subgroups.[83] Efficacy was similar when binimetinib was added to the encorafenib plus cetuximab regimen and both regimens had significantly improved efficacy and quality of life assessments relative to the control in patients with *BRAF* V600E-mutated mCRC whose disease had progressed after one or two prior regimens.[70,80,81,83] In the updated analysis, confirmed ORR results by blinded independent review based on all randomized patients were 26.8% (95% CI 21.1% to 33.1%) for triplet, 19.5% (95% CI 14.5% to 25.4%) for doublet, and 1.8% (95% CI 0.5% to 4.6%) for control.[83] For median PFS, the updated results were 4.5 months (95% CI 4.2-5.4 months), 4.3 months (95% CI 4.1-5.4 months), and 1.5 months (95% CI 1.5-1.9 months) for triplet, doublet, and control, respectively, with HRs of 0.42 (95% CI 0.33-0.53) and 0.44 (95% CI 0.35-0.55) for the triplet and doublet, respectively, compared with the control.[83] These data compare favorably with the prior results from studies of irinotecan and cetuximab with or without vemurafenib.[59,79] The safety and tolerability profiles of both the triplet and the doublet combinations were consistent with the known profiles of the component agents.[70] Grade 3 or higher adverse events were seen in 58% of patients who received the triplet regimen, 50% of those in the doublet group, and 61% of those in the standard-therapy group. Both experimental treatment arms had similar rates of adverse events, and the frequency of grade 3 or higher toxicity was slightly higher in the control arm than in either targeted therapy treatment arm, with a median duration of exposure to study treatment of 21, 19, and 7 weeks in the triplet, doublet, and control arms, respectively. Binimetinib as part of the triple combination does add some additional toxicity associated with MEK inhibition. Overall, anemia, dermatitis acneiform, diarrhea, nausea, and vomiting (all grades) were reported at a higher incidence (>10.0% difference in incidence) in the triplet arm than in the doublet arm, whereas headache and melanocytic nevus were reported at a higher incidence in the doublet arm than in the triplet arm.

These outcomes represent the first survival benefit in this patient population and an improvement over the current standard of care. The results of the BEACON CRC study provide support for encorafenib plus cetuximab to be a new standard of care for patients with mCRC with a *BRAF* V600E mutation who have received prior systemic therapy. The FDA and European Commission approved the doublet regimen for the treatment of *BRAF* V600E-mutated mCRC after prior therapy in April and June 2020, respectively. At the same time, the FDA approved a therascreen *BRAF* V600E Rotor-Gene-Q PCR assay as a companion diagnostic to encorafenib. The doublet and triplet regimens are both approved for use in Japan for the treatment of *BRAF* V600E-mutated mCRC. Some patient populations may benefit more from triplet than doublet therapy, as suggested by exploratory subgroup analyses (such as patients with involvement of more than two organs and patients with high C-reactive protein levels at baseline), but they should only be considered hypothesis generating until further prospective research is available to validate these observations. At this time, the combination of encorafenib plus cetuximab is considered the standard of care for second- and third-line *BRAF* V600E-mutated mCRC, irrespective of the patient's clinical characteristics. Accrual for a single-arm study to evaluate the triplet regimen in the first-line setting was recently completed [encorAfenib, biNimetinib and Cetuximab in subjects witH previOusly untreated BRAF-mutant ColoRectal Cancer (ANCHOR CRC), NCT03693170]. In the first 40 assessable patients from ANCHOR CRC, investigator-assessed confirmed ORR was 50% (95% CI 33.8% to 66.2%) and median PFS was 4.9 months (95% CI 4.4-8.1 months). A decrease in tumor size was observed in 85% of patients. Adverse events have been consistent with those observed in prior studies of the triplet combination.[84]

EVIDENCE-BASED GUIDELINE RECOMMENDATIONS

The NCCN has published updated guidelines with specific testing and treatment recommendations related to *BRAF*-mutant mCRC. For testing, the NCCN recommends that all patients with mCRC should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of a next-generation sequencing (NGS) panel.[49] Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor. In the United States, testing for *KRAS*, *NRAS*, and *BRAF* mutations should be carried out only in laboratories that are certified under the

clinical laboratory improvement amendments of 1988 as qualified to perform 'high-complexity' clinical laboratory (molecular pathology) testing. No specific methodology, such as sequencing or hybridization, is recommended. The testing can be carried out on the primary CRCs and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.

The NCCN panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be carried out on formalin-fixed paraffin-embedded tissues and is usually carried out by PCR amplification and direct DNA sequence analysis. Allele-specific PCR, NGS, and immunohistochemistry are other acceptable methods for detecting this mutation.[49]

Current NCCN consensus guidelines recommend combination chemotherapy for first-line treatment for patients with mCRC and a suitable performance status, including those with a *BRAF* mutation. First-line chemotherapy options generally include irinotecan- or oxaliplatin-based combinations.[49] Bevacizumab may also be added, as previously discussed.

Following progression of *BRAF* V600E-mutated mCRC after first-line treatment, subsequent systemic therapy recommendations from the NCCN include the combination of encorafenib in addition to EGFR inhibition with cetuximab or panitumumab.[49] Triplet regimens containing dabrafenib plus trametinib plus cetuximab or panitumumab and encorafenib plus binimetinib plus cetuximab or panitumumab were removed as treatment options for *BRAF* V600E-mutated mCRC in the latest version of the NCCN guidelines. The NCCN based this recommendation on results from the BEACON CRC trial.[49,70,81]

It should be recognized that among patients with colorectal liver metastasis who undergo hepatectomy, those with *BRAF* V600E-mutated cancer have a higher risk of recurrence and death than those with *BRAF* WT cancer.[85] Nonetheless, some patients with *BRAF* V600E mutations may derive prolonged survival or cure from curative surgical resection of metastases. Current guidelines do not call for withholding interventions with curative intent for patients with oligometastatic *BRAF* V600E-mutated disease.[49]

FUTURE PERSPECTIVES AND SUMMARY

The treatment of *BRAF*-mutated CRC has evolved rapidly over the last several years. Combination strategies involving MAPK pathway blockade have shown promising results for the treatment of patients with *BRAF* V600E-mutated mCRC. The BEACON CRC study represents the largest study in this population to date and has given strong clinical evidence to support BRAF and EGFR inhibition with the combination of encorafenib plus cetuximab. The ANCHOR study will provide insight into the activity of the combination of encorafenib, binimetinib, and cetuximab in patients with previously untreated *BRAF* V600E-mutated mCRC. Based on the good side-effect profile, additional research includes a first-line evaluation of the BEACON CRC doublet (encorafenib/cetuximab) as purely biologic therapy and in combination with chemotherapy [BRAF V600E-mutant colorectal cancer study evaluating EncorAfenib taKen With cetuximAb plus or minus chemoThERapy (BREAKWATER) (NCT04607421)], and may include an evaluation of the BEACON doublet in the adjuvant setting. In an effort to continue to improve outcomes, other potential targets are being explored, taking advantage of other unique molecular characteristics of *BRAF*-mutated mCRC tumors. Given the enrichment of *BRAF* V600E mutations within CMS subtype 1 CRCs, there is significant interest in combining anti-programmed cell death protein 1 (PD-1) treatments with BRAF/EGFR-targeting therapies (e.g. NCT0404430). Additional investigations incorporate various combinations of BRAF, MEK, ERK, CRAF, SHP2, and PD-1 inhibitors (e.g. NCT04294160). Future research should also include a continued focus on developing treatments that overcome mechanisms of resistance. An enhanced understanding of the role of the *BRAF* V600E mutation in the pathogenesis of mCRC will extend the recent treatment advances and further improve outcomes for patients.

ACKNOWLEDGMENTS

Medical writing/editorial support was provided by J. D. Cox, PhD, at Mayville Medical Communications and was funded by Pfizer.

FUNDING

This work was supported by Array BioPharma, which was acquired by Pfizer in July 2019 (no grant number).

DISCLOSURE

AG: Honoraria from Aptitude Health and Elsevier; consulting or advisory role (fees paid to institution): Amgen, Array BioPharma, Bayer, Boston Biomedical, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Genentech, and Guardant Health; research funding (fees paid to institution): Array BioPharma, Bayer, Boston Biomedical, Daiichi Sankyo, Eisai, Eli Lilly, Genentech, and Pfizer; fees for travel/accommodation/expenses: Amgen, Bayer, Boehringer Ingelheim, Boston Biomedical, Bristol Myers Squibb, Genentech, and Merck Sharp & Dohme. MF: Honoraria from Amgen; consulting or advisory role: Amgen, Array BioPharma, Bayer, Pfizer, Seattle Genetics, and Taiho; speaker bureau: Amgen and Guardant360; research funding (fees paid to institution): Amgen, AstraZeneca, and Novartis. JT: Consulting or advisory role: Array BioPharma, AstraZeneca, Bayer, BeiGene, Biocartis, Boehringer Ingelheim, Chugai Pharma, Eli Lilly, Foundation Medicine, Genentech, Genmab, HalioDX SAS, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura, Menarini, Merck Serono, Merck Sharp & Dohme, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, Roche, Roche Diagnostics, Sanofi, Seattle Genetics, Servier, Symphogen, Taiho Pharmaceutical, and VCN Biosciences.

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