REVIEW ACHAIKI IATRIKI | 2022; 41(3):146–153

BRAF positive colorectal cancer

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Abstract

Colorectal cancer constitutes a clinical entity affecting many people with a risk increasing through somebody's lifetime. Early diagnosis is still the most significant factor for a successful outcome thus the role of screening colonoscopy in asymptomatic individuals remains paramount. As clinical experience and research on this disease becomes broader and deeper, we are becoming increasingly aware of the distinct biological phenomena that take place and the various patients' subgroups. This expanding knowledge sheds light on the diversity of the clinical scenarios and outcomes we observe in real practice. One of the molecular and pathophysiological events that takes place is the dysregulation of the EGFR/MAPK pathway, which involves molecules such as the RAS and the BRAF proteins. The significance of these molecules and their accountable genes' mutations is now ever more studied and understood. Gene expression analysis has classified CRC according to the various molecular alterations and their clinical associations in four distinct groups (consensus molecular subgroups, CMS1-4). *BRAF* mutations, especially the dominant *V600E* mutation, has been correlated to a more aggressive phenotype and poor outcome (CMS1). Fortunately, great steps in the management of this unique patients' group have been achieved and novel successful approaches have been found while research is ongoing.

Key words: *Colorectal cancer; molecular alterations; BRAF mutation*

INTRODUCTION

Colorectal cancer (CRC) is the third commonest cancer in males and females respectively, following breast, lung and prostate, and the second commonest cause of death among all cancer patients worldwide [1]. Our understanding regarding colorectal cancer's etiology has been evolving over the last 20 years leading to changes and advances in its treatment. We have reached now the era of individualized and tailored management, where apart from the classic and paramount clinical judgement various specific genomic alterations help to select the appropriate strategy for the different patient sub-populations and each individual patient accordingly.

The main biological pathway of CRC carcinogenesis is through the signaling cascade RAS/RAF/MEK/extracellular signal-regulated kinase (ERK), also known as the mitogen-activated protein kinase (MAPK) pathway that starts from the transmembranic epidermal growth factor receptor (EGFR) pathway (Figure 1). In normal cells, this pathway drives cell proliferation and differentiation and additionally their migration, survival and angiogenesis. This cascade is composed of the RAS small proteins [guanidine triphosphatase (GTPase)], which activate the RAF family proteins (mainly BRAF) and subsequently lead to the phosphorylation and activation of MEK1/2 proteins and ERK. Dysregulation of this pathway often leads to uncontrolled proliferation and tumorigenesis [2,3].

The percentage of RAS mutations' detection in all colorectal cancers varies from 9%–30% whereas BRAF mutations are found in 7% of all cancers (including early-stage disease) but in 8%-12% of metastatic CRC, with BRAF V600E accounting for >90% of mutations in BRAF-mutated cancers [4,5]. The mutated gene mimics regulatory phosphorylation with a 10-fold increase in BRAF activity compared with the wild-type. In contrast to the dominant activating BRAF V600E mutation, there

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Received: 09 Jan 2022; Accepted: 11 May 2022

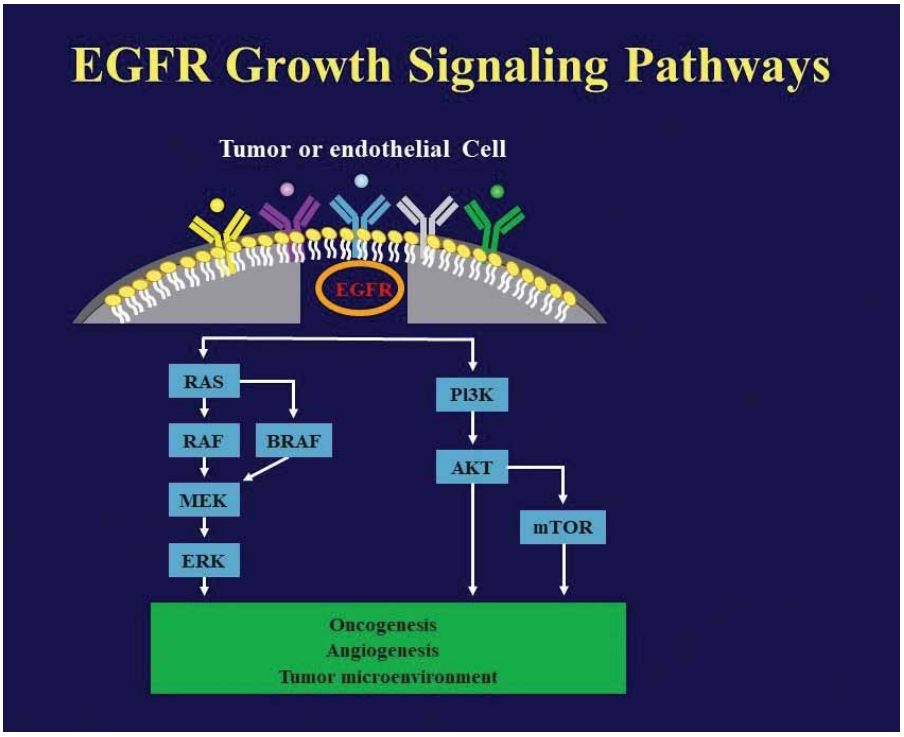

Figure 1. The molecular pathways of EGFR.

are other less common ones such as BRAF D594G or G596N, which are kinase-impairing mutations. Patients with $^{non\text{-}V600E}$BRAF-mutant metastatic colorectal cancer are younger, with fewer high-grade and right sided tumors. They also show a significant longer median overall survival and a better prognosis [6,7]. In this review though, we will focus on the commonest V600E mutation and its role in CRC.

Genetic abnormalities and molecular classification in CRC

Most colon cancer cases, namely about 80% of cases, are sporadic. The remaining 20% are familial or related to specific genetic syndromes such as familiar adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal carcinoma (HNPCC) which account for about 1% and 5% of all CRC cases respectively. FAP is associated with mutations of the *adenomatous polyposis coli* (*APC*) gene whereas HNPCC with germline mutations of mismatch repair (MMR) genes (mainly *hMSH2*, *hMSH6, hMLH1*) [8].

The majority (85%) of genetic changes occurring in CRC are due to chromosomal instability (CIN). CIN has long been reported as a key genetic abnormality having a dominant effect in colorectal carcinogenesis following the traditional adenoma-carcinoma model [9]. The alternative serrate adenoma to adenocarcinoma pathway (around 10% of cases) is characterized by microsatellite instability (MSI).

Serrated tumours are not chromosomal instable but often exhibit extensive DNA methylation of CpG islands. This methylation may occur in the *MLH1* promoter (a gene of the mismatch repair system) leading to the 'sporadic' microsatellite instable (MSI) phenotype.

Mutations in the *BRAF* gene in CRC pathogenesis develop within the serrated pathway. Tumours 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. Quite recently, using cutting edge technology (Next generation sequencing, NGS) four distinct subgroups [known as the consensus of molecular subtypes (CMS)] were identified in CRC based on intrinsic gene expression profile patterns (Table 1). The majority of *BRAF*-mutant CRCs are CMS subtype 1 (MSI high, immune) and are associated with deficient DNA repair, hypermethylation, and a high mutational burden [9,10].

Additionally, two new subtypes of *BRAF*-mutant CRC

Table 1. *Consensus Molecular Subtype Classification (CMS).*

Subtype	Biological findings	Clinical findings	Prognosis	Incidence
CMS 1 Immune	MSI high BRAF mutated Hypermutations (high TMB) Immune activation	Right sided Females Older age	Intermediate to poor survival	~ 14%
CMS 2 Canonical	CIN high ↑ EGFR activation MSS TP53 mutation ↑↑ WNT/MYC activation	Left sided	Good	~ 37%
CMS 3 Metabolic	CIN low KRAS mutation PI3K mutations Metabolic dysregulation		Intermediate	~ 13%
CMS 4 Mesenchymal	CIN high Notch3/VEGFR2 overexpression ↑ TGF-beta activation Stroma infiltration Angiogenesis	Younger age	Poor survival and worse relapse free survival	23%
Mixed	Intratumoral heterogeneity	Transition phenotype		13%

classification, BM1 and BM2, have also been proposed based on differential gene expression with distinct molecular patterns [10]. BM1 is characterized by *KRAS/AKT* pathway activation, mTOR (mammalian target of rapamycin) deregulation, and epithelial–mesenchymal transition-related (EMT) processes with *KRAS* signaling and immune response, whereas BM2 is characterized by deregulation of the cell cycle and cycle checkpoint-related processes [10]. The presence of two subgroups of *BRAF*-mutant CRC may help explain the differences in response to treatment among various patients and their diverse outcome. BM1 has a worse prognosis and a different approach in treatment is recommended compared to BM2. For instance, targeting the EGFR downstream cascade may provide greater benefit to BM1 compared to checkpoint-CDK inhibition that may offer more benefit to BM2 [10].

Finally, overlapping between MSI and *BRAF* mutation often occurs in this population. In the era of immunotherapy in cancer, anti-PD1 drugs have been approved in MSI tumours including mCRC. However, the role of these antibodies in MSI *BRAF*-mt mCRC is still to be determined. Therefore, the best sequence (targeted therapy or checkpoint inhibitors) is still to be determined in the future.

Clinical implications of BRAF mutations

Clinically, *BRAF*-mt CRC has been associated with a more advanced age of diagnosis and female sex, proximal (right) colon tumors, poorer differentiation, mucinous histology, MSI high and larger primary tumors. The pattern of metastatic spread seems also to differ compared to *BRAF* wildtype (*BRAF*-WT) tumours with more peritoneal metastases seen in BRAFmt and fewer liver-only and lung metastases [11,12].

BRAF mutation confers worse prognosis in the metastatic setting. In a pooled analysis of some of the largest phase III studies in metastatic CRC (the FOCUS, COIN and CAIRO I and II trials) worse OS for *BRAF*-mt CRC as compared to the *BRAF* wild type (WT) counterparts has been reported [13].

Survival in *BRAF*-mt populations after lung or liver metastasectomy has been also studied and results confirm worse prognosis and shorter OS after surgery compared with *KRAS*-mt or -BRAF WT tumors [14,15].

The poor prognosis of *BRAF V600E*-mutant mCRC has

been attributed to various biological phenomena such as aberrant programmed cell death or the suppressed expression of CDX2 (caudal type homeobox 2) [16]. CDX2 is a tumor suppressor and transcription factor involved in the regulation of intestinal epithelial cell differentiation, cell adhesion, and polarity and the loss of CDX2 has been associated with metastasis and poor prognosis in CRC [17]. Given their overall favourable prognosis in earlier stages, MSI-H tumors may attenuate the adverse prognostic impact of *BRAF* mutations [18]. *BRAF*-mutated MSI-H tumors have a less aggressive clinical phenotype and improved OS compared to *BRAF*-mutant MSS tumors [13].

Although chemotherapy has significantly improved overall survival (OS) in CRC, response and treatment benefit appear lower for *BRAF*-mt tumors both at earlier and advanced disease stages.

Whether BRAF can serve as a predictive biomarker of response to chemotherapy this has been long debated with early evidence from retrospective and phase II data suggesting patients with *BRAF*-mt CRC do better with intensive regimens such as FOLFOXIRI-bevacizumab though no confirmation from the phase III TRIBE 3 study was found for this particular population. It has been postulated that the small numbers of BRAFmt patients in these studies don't help us draw safe conclusions [19,20].

On the other hand, we know that treatment with monoclonal antibodies targeting the EGF receptor (cetuximab and panitumumab) in the *RAS*-WT patients' population is not that effective in the presence of *BRAF* mutations according to meta-analyses of many clinical trials [21,22].

Treatment of BRAF mutant CRC

Since no data have shown any role of targeting the BRAF protein during the early stage of the disease we will focus here on the metastatic setting where intensive research has taken place over the last decade.

Based on the positive experience and the successful results with BRAF inhibitors in BRAF V600E positive melanoma many clinical studies tested their usefulness in metastatic CRC. Disappointingly enough there was no similar to melanoma benefit from monotherapy with the BRAF inhibitors vemurafenib, dabrafenib or encorafenib in pretreated CRC patients probably due to the presence of resistance mechanisms or the complexity of involved pathways rather than a targetable point mutation. The main studies in BRAF mutant CRC patients and the efficacy of the tested agents or regimens are summarized in Table 2. Since monotherapies did not produce positive results, combinational strategies were planned and indeed a better outcome was reported when BRAF inhibitors were combined with EGFR inhibitors (cetuximab – panitumumab), MEK inhibitors (trametinib, binimetinib) or a PI3K inhibitor (alpelisib) in double or triple regimens.

The first meaningful clinical results were derived from the phase II SWOG 1406 study where vemurafenib with cetuximab plus irinotecan showed that triple therapy was associated with an objective response rate of 16% and a PFS of 4.4 months [23]. 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 [24].

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 showed a better response rate (ORR) for the triplet therapy, but at the cost of more adverse events mainly grade 3/4 diarrhea compared to the doublet treatment [25]. Lately, combination of encorafenib and cetuximab versus encorafenib, cetuximab, and the PI3K inhibitor alpelisib were evaluated in a phase Ib dose-escalation study in 28 patients with refractory *BRAF*-mutated CRC. The authors reported an 18% ORR and a disease control rate of 93% for the triplet regimen of encorafenib, cetuximab, and alpelisib [26]. These results were reproduced in a subsequent phase II study in 52 patients treated with these regimens and additionally the PFS was numerically higher for the triplet compared to the doublet regimen (5.4 months versus 4.2 months) [27]. As expected, the frequency of adverse events with the triplet was higher, mostly anaemia, hyperglycemia, and increased serum lipase levels [27].

Finally, the most significant results available today came from the phase III BEACON 3-arm trial that was published in 2019, in patients with *BRAF* V600E-mutated mCRC who had had disease progression after one or two previous treatment regimens (28). A total of 665 patients were randomized 1 : 1 : 1 to receive encorafenib, cetuximab, and binimetinib (a MEK inhibitor) (arm A) versus encorafenib and cetuximab (arm B) versus irinotecan or FOLFIRI plus cetuximab (arm C) [28]. Almost all patients had previously received oxaliplatin and half of patients had previously received irinotecan before enrolment

Table 2. *Main studies of BRAF inhibitors in metastatic CRC.*

Regimen (Author, reference)	RR, %	mPFS, mo
Single/Doublet BRAF/MEK		
Vemurafenib (Kopetz S. JCO 2015)	5	2.1
Dabrafenib (Falchook GS. Lancet 2012)	11	NR
Encorafenib (Gomez-Roca C. ESMO 2014)	6	4
Dabrafenib + Trametinib (Concoran R. JCO 2015)	12	3.5
Doublet with EGFR		
Vemurafenib + Panitumumab (Yaeger R. Clin Ca R 2015)	13	3.2
Vemurafenib + Cetuximab (Tabernero J. ASCO 2014)	20	3.2
Encorafenib + Cetuximab (van Geel R. Canc Disc 2017)	19	3.7
Dabrafenib + Panitumumab (Atreya CE, ASCO 2015)	10	3.4
Triplet with EGFR		
Vemurafenib + Cetuximab + Irinotecan (Hong D. Cancer Discov 2017)	35	7.7
Dabrafenib +Trametinib + Panitumumab (Atreya CE, ASCO 2015)	26	4.1
Encorafenib + Cetuximab + Alpelisib (van Geel R. Cancer Discov 2017)	18	4.2
Encorafenib + Cetuximab +/- Binimetinib vs Cetuximab + Irinotecan or FOLFIRI (Kopetz S. NEJM 2019)	26.8 / 19.5 vs 1.9	4.5 / 4.3 vs 1.5 **[mOS: 9.3/9.3 vs 5.9]**
Encorafenib + Cetuximab + Binimetinib (1st line) (Van Cutsem E. ESMO 2021)	47.5	5.8

into this study. This trial is the largest ever conducted in this population and the first phase III trial to show both a survival and response advantage in pre-treated *BRAF*-mutated CRC patients. The primary endpoints for the BEACON CRC study were overall survival (OS) and blinded central review confirmed objective response (ORR) for the triplet combination (arm A) compared with the control arm C. A key secondary endpoint was OS for the encorafenib plus cetuximab (doublet) regimen versus control. Other secondary endpoints included progression free survival (PFS), duration of response, and safety [28].

The mature results of the BEACON CRC study showed that the encorafenib plus cetuximab regimen significantly improved OS compared 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) [29]. Efficacy was similar when binimetinib was added to the encorafenib plus cetuximab regimen (9.3 months OS) and both regimens (arms A & B) had significantly improved efficacy and quality of life (QoL) assessments relative to the control in patients with *BRAF* V600E-mutated mCRC whose disease had progressed after one or two prior regimens [29]. On the Patient Global Impression of Change scale, more than 20% of the patients in arm B and arm A said they were "very much improved," compared with 10% of those on the control arm C [30]. 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. For median PFS, the updated results were 4.5 months (95% CI 4.2-5.4 months) in arm A, 4.3 months (95% CI 4.1-5.4 months) in arm B, and 1.5 months (95% CI 1.5-1.9 months) in arm C, respectively,

with HRs of 0.42 (95% CI 0.33-0.53) and 0.44 (95% CI 0.35-0.55) for arms A and B, respectively, compared with the control arm C. These data are comparable to earlier results from studies of irinotecan and cetuximab with or without vemurafenib. The safety and tolerability profiles of both investigational combinations were consistent with the known profiles of the involved agents with more grade 3 or higher adverse events being seen in arm A (58%) than arm B (50%) but almost similar to standard arm C (61%). Binimetinib as part of the triple combination does actually add some additional toxicity associated with MEK inhibition. Overall, side effects such as anaemia, dermatitis acneiform, diarrhoea, nausea, and vomiting were reported at a higher incidence of more than 10.0% difference in arm A than in arm B, whereas headache and melanocytic nevus were reported at a higher incidence in the doublet arm than in the triplet arm [29].

The results of the BEACON CRC study set the basis of a new standard of care in this pre-treated patient population as it is the first trial that provided a meaningful survival benefit and an improvement over the till now standard of care. Based on the more tolerable toxicity profile the American and European Authorities approved the doublet regimen for the treatment of *BRAF* V600E-mutated mCRC after prior therapy.

A single-arm phase II first-line study (ANCHOR CRC) [encorAfenib, biNimetinib and Cetuximab in subjects witH previOusly untreated BRAF-mutant ColoRectal Cancer] was recently completed and evaluated the triplet regimen in this setting [31]. The findings after 92 patients from ANCHOR CRC were assessed were very positive, and the investigator-assessed confirmed ORR was 47.5% (95% CI 37.3 - 58.2), the disease control rate (DCR) reached 88% while the median PFS was 5.8 months (95% CI 4.6-6.4 months) and the reported OS 17.2 months (95% CI 14.1-NE). Grade 3 or higher adverse events were reported by almost 70% of patients, in particular anaemia (10.5%), diarrhoea (9.5%), nausea (8.4%) bowel obstruction (6.3%) and renal injury (5.3%) and have been consistent with those observed in prior studies [31].

These encouraging results emphasize the need for further exploration and confirmation thus the phase III study BREAKWATER is now in progress and will test the efficacy of encorafenib plus cetuximab with or without chemotherapy as a first line treatment of BRAF V600E mutant untreated CRC patients [32].

As far as the $^{\text{non-V600E}}$ BRAF mutant patients are concerned, better outcome and potential response to antiEGFR therapy has been suggested in preclinical, early phase studies and case reports [33-35].

CONCLUSIONS

The role and significance of BRAF mutations in colorectal cancer is now well accepted. 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 represented the largest phase III 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. Based on these results we have a new standard of care in 2nd or 3rd line treatment, in *BRAF* V600E-mutated patients.

The ANCHOR phase II study suggested similar activity of the doublet (encorafenib/cetuximab) in the first line setting. So, it will be much anticipated to see the outcomes of the phase III BREAKWATER first line study [BRAF V600E-mutant colorectal cancer study evaluating encorafenib taken with cetuximab plus or minus chemotherapy (NCT04607421)] and if positive the BEACON doublet regimen may even deserve an evaluation in the adjuvant setting. In future, other potential targets might be explored, taking advantage of other unique molecular characteristics of *BRAF*-mutated mCRC tumors as defined by the gene expression profiling. Given the enrichment of *BRAF* V600E mutations within CMS subtype 1 CRCs, there is a 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 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 eventually expand recent treatment advances and further improve outcomes for patients. When possible, the non-V600E BRAF mutations should be sought and when clinically appropriate, patients may be given the opportunity of anti-EGFR treatment. In any case this sub-population requires separate clinical studies.

Conflict of interest disclosure: *None to declare*

Declaration of funding sources: *None to declare*

Author Contributions: *Alexios S. Strimpakos is the sole author of this work.*

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