Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E-Mutated Colorectal Cancer

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ABSTRACT

BRAFV600-mutated colorectal cancer (CRC) accounts for 8% to 12% of all CRC diagnoses. These tumors are often associated with specific patient features, including right-sided primary tumor location, peritoneal and non-regional lymph node involvement, and poor prognosis. In approximately 30% of cases, a simultaneous mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) phenotype is identified. The prognostic impact of the BRAF mutation appears to be less marked in patients with MSI-H CRC than in patients with microsatellite stable (MSS) tumor. The treatment of BRAFV600-mutated CRC is still a challenge for the clinicians, mainly due to the poor survival outcomes obtained with traditional chemotherapy regimens.

In recent years, two novel treatment strategies have offered remarkable changes in the treatment of this specific patient subgroup. The first approach has included targeted therapies directed against BRAF and MEK, with support from the epidermal growth factor receptor (EGFR) blockade. The second approach has included immunotherapeutic agents that have been shown to be particularly promising for patients with simultaneous dMMR/MSI-H phenotype.

Here we review the clinical trials that specifically enrolled patients with BRAF-mutated CRC, from the phase I/II studies to the phase III trial BEACON CRC. We also examine the future directions towards a molecularly guided therapy for patients with BRAF-mutated CRC and the crucial role of a molecularly and clinically based algorithm in order to offer the best choice of treatment for these patients.

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, with over 1.800.000 new cases every year in the world. With approximately 881.000 deaths annually, CRC accounts for nearly 85% of all cancer-related deaths [1]. Unfortunately, 20% to 30% of CRC diagnoses occur at a late stage of the disease when upfront surgery is no longer indicated. A larger proportion of metastatic CRC (mCRC) diagnoses include patients who have developed metachronous metastases after radical surgery. [2–4].

In the past decades, the treatment of patients with mCRC has been successfully improved through the introduction of monoclonal antibodies (MoAbs) against the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathways [5,6].

A more accurate molecular selection of patients has been implemented, at first with the identification of the RAS status as a predictive biomarker of response to anti-EGFR MoAbs [7,8] and, in the last few years, with the identification of other specific subgroup of patients whose tumors have mutations in BRAF, human epidermal growth factor receptor 2 (HER2), HER3 or PIK3CA, amplification of HER2, HER3 or MET, PTEN loss, NTRK alterations, or a mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) phenotype. [9–13].

BRAFV600-mutated CRC accounts for 8% to 12% of all CRC diagnoses. These cancers are often associated with specific patient features, including right-sided primary tumor location in approximately 60% of cases, development of peritoneal and non-regional distant lymph node metastases, and dMMR/MSI-H phenotype in approximately 30%. [12–14].

Several mechanisms are responsible for the MSI-H phenotype, including inactivation of the MLH1, MSH2, MSH3, MSH6 and PMS2 genes, epigenetic inactivation, and downregulation by microRNAs. Overall, hypermethylation of the MLH1 promoter is the primary mechanism for MSI-H in sporadic CRC including BRAF-mutated CRC. [13,14]

Taken together, the BRAFV600-mutated CRCs are associated with a worse prognosis. However, the prognostic impact of the BRAF mutation appears to be less marked in patients with MSI-H CRC than in patients with microsatellite stable (MSS) phenotype [13,14]. In a pooled analysis that included four phase III studies (CAIRO, CAIRO2, COIN, and FOCUS), among patients with proficient mismatch repair (pMMR) CRC, a decreased survival was observed for patients with BRAF-mutated tumor compared to those with BRAF wild-type (WT) tumor. In specific, progression-free survival (PFS) was 6.2 and 7.8 months (HR 1.34, $P < .001$), respectively, and overall survival (OS) was 11.3 vs 17.3 months (HR 1.94, $P < .001$), respectively [13]. Another pooled analysis evaluated the prognostic value of BRAF-V600E mutations among operated stage III CRC patients. The group of patients with BRAF-mutated CRC was associated with a shorter median OS ($P < .001$) and time to recurrence ($P = .02$) compared with the BRAF WT group. In specific, BRAF mutation was a negative prognostic factor for OS ($P < .001$) and time to recurrence ($P < .001$) among patients with MSS cancer. In contrast, among MSI-H patients, there was not a statistically significant difference in terms of time to recurrence ($P = .80$) and OS ($P = .35$) according to BRAF status. [14]

A distinct smaller patient subgroup, usually associated with a better prognosis, is represented by non-V600 BRAF-mutated CRC. In approximately 2% of all CRC cases, indeed, BRAF mutations occur outside of codon 600. Patients with non-V600 BRAF-mutated CRC are more frequently associated with younger age ($P < .001$), male gender ($P < .001$), low-grade cancers ($P < .001$), left-sided primary tumor location ($P < .001$), and lower probability to develop peritoneal metastases ($P < .001$), compared with those with BRAF-V600 mutated CRC. In a retrospective analysis, non-V600 BRAF-mutated CRC was also associated with longer median OS (60.7 months) compared with BRAFV600-mutated CRC (11.4 months, $P < .001$) and BRAF WT CRC (43.0 months, $P < .001$) [15].

In addition to the well-known negative prognostic value, BRAF-V600 mutations have also been reported to be a putative predictive biomarker of responsiveness to anti-EGFR MoAb. Pietrantonio and colleagues included nine phase III trials and one phase II trial in a meta-analysis to demonstrate whether there was a benefit from adding the anti-EGFR MoAbs to chemotherapy in patients with BRAF-mutated CRC. The meta-analysis showed no statistically significant benefit from adding panitumumab or cetuximab to chemotherapy for this patient population. No benefit was observed in terms of PFS (HR 0.88; $P = .33$), OS (HR 0.91; $P = .63$), and overall response rate (ORR) (relative risk 1.31; $P = .25$) for anti-EGFR MoAb-based regimen compared with chemotherapy alone [16]. Another meta-analysis included seven phase III studies to evaluate the effect of BRAF mutations in patients treated with anti-EGFR MoAb-based regimens. Although a clear difference in HR values (HR 0.98 for the RAS WT/BRAF-mutated CRC group vs 0.81 for the RAS and BRAF WT CRC group), the interaction test for OS was not statistically significant across the two subgroups ($P = .43$). Therefore, the meta-analysis concluded that there was insufficient evidence to demonstrate a profoundly different benefit from anti-EGFR therapy according to BRAF mutational status. [17]

In the TRIBE trial, the BRAF-V600 mutations were a negative prognostic factor for survival outcomes. Patients with BRAF-mutated CRC had a median OS of 13.4 months compared with 37.1 months in those with BRAF and RAS WT CRC and 25.6 months in those with RAS-mutated CRC. Although BRAF-mutated patients had a poor prognosis, median OS and PFS were 19.0 and 7.5 months, respectively, among those treated with FOLFOXIRI bevacizumab regimen, compared with 10.7 and 5.5 months in the control arm. The triplet-therapy has been shown to be effective across all molecular subgroups, improving both OS and PFS, with p values for the interaction of 0.52 and 0.68, respectively. Since the publication of the TRIBE trial, therefore, the FOLFOXIRI bevacizumab regimen has been considered the preferred first-line treatment in fit patients with advanced BRAFV600-mutated CRC [18].

Role of BRAF Mutation

BRAF was identified as an oncogene in human cancer and its mutations, which mainly occur within the kinase activation domain, result in constitutive activation of the MEK-/ERK-signaling pathway. [19] (Figure 1). BRAF is a member of the RAF kinases group that also includes CRAF and ARAF. RAF kinases generally promote the activation of the MAPK signaling pathway after the activating signal from RAS. In turn, RAF kinases activate by phosphorylation MEK 1 and MEK 2 (MEK kinases) that finally sustain ERK1 and ERK2 (ERK kinases) activation, resulting in phosphorylation of various cellular substrates with pivotal roles in cell survival and proliferation [20]. The constitutive BRAF kinase activation and the following MEK and ERK kinases activation plus the activated MAPK pathway are supported by BRAF-V600 mutations.

BRAF mutations are related to negative clinical outcome in CRC patients with increased mortality of nearly 70% at the metastatic stage if compared to BRAF wild type patients [21]. In 2011, the FDA approved the discriminating RAF inhibitor vemurafenib (PLX4032) for the treatment of BRAF V600-mutated metastatic melanomas; even though inhibitors of BRAF showed clinical efficacy in BRAF V600E-mutated melanomas with a remarkable response rate of nearly 70%, BRAF inhibitors showed only limited efficacy in BRAF V600E-mutated CRC [22–23]. Preclinical studies of BRAF V600-mutated CRCs have reported
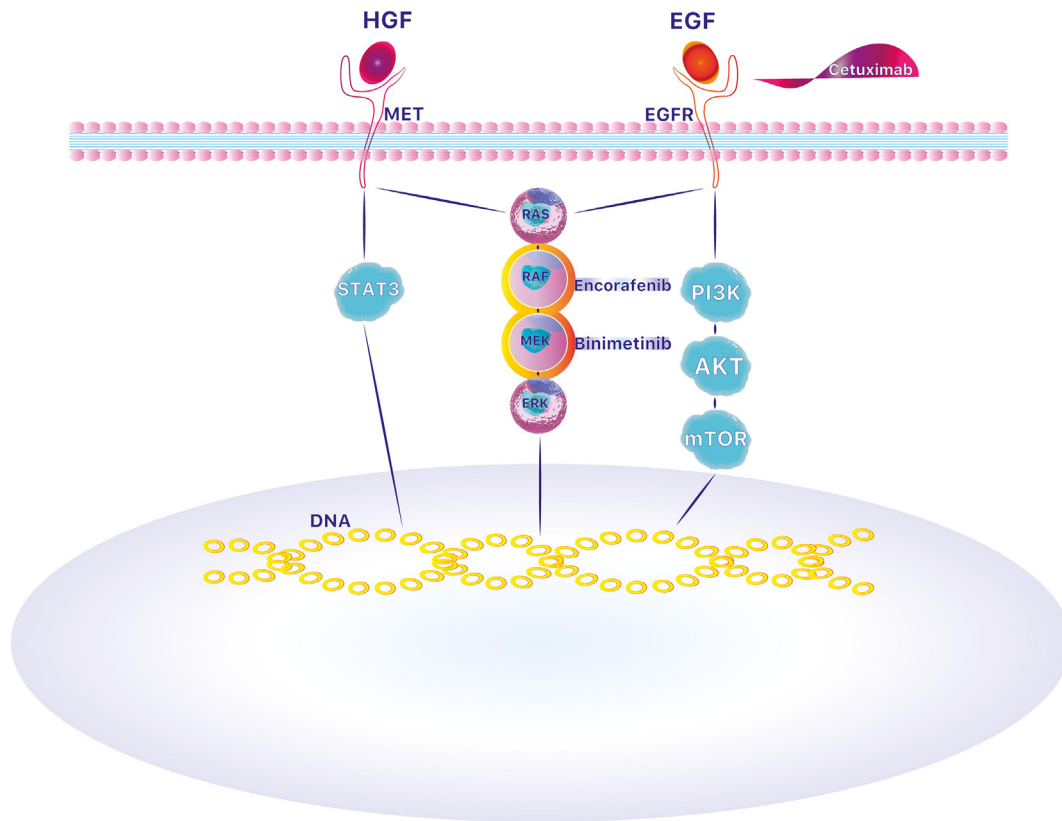
Figure 1. Mechanism of action of cetuximab, encorafenib and binimetinib. BRAF is a member of the RAF kinases group. RAF kinases generally promote the activation of the MAPK signaling pathway after the activating signal from RAS. In turn, RAF kinases activate by phosphorylation MEK 1 and MEK 2 (MEK kinases) that finally sustain ERK1 and ERK2 (ERK kinases) activation, resulting in phosphorylation of various cellular substrates with pivotal roles in cell survival and proliferation.

a rapid feedback activation of EGFR as a result of BRAF inhibition, suggesting that BRAF inhibitors alone are not sufficient to suppress pathway signaling, which in turn clarifies the lack of clinical efficacy of BRAF inhibition in CRC patients [24].

This question has been partly addressed by the fact that EGFR is mainly expressed in epithelial cancers—such as CRC—whereas melanomas derived from the neural crest; therefore, the advantageous outcome of melanomas with vemurafenib treatment might occur due to the scarce amount of EGFRs and the consequent absence of feedback activation of EGFR on these tumors [24]. Besides, researchers showed that vemurafenib led to a constitutive P-ERK suppression in melanoma cell lines but only a transient P-ERK suppression in CRC lines, with a recovery of P-ERK levels up to 50% in 24 hours, giving a reason of MAPK pathway re-activation in CRC lines [25]. This P-ERK rebound in BRAF-mutated CRC lines consequent to the vemurafenib treatment has been correlated to the induction by phosphorylation at site S338, and the consequent activation, of the CRAF kinase [25]. However, it has also been showed that the supplementation of the MEK inhibitor AZD6244, also known as selumetinib, could block P-ERK rebound after RAF inhibition, suggesting that the P-ERK rebound is MEK-dependent [25]. Interestingly, a certain difference has been observed with BRAF inhibitors in other neoplasia such as melanoma compared with CRC. While vemurafenib more durably inhibits phospho-ERK in CRC versus melanoma, in melanoma this inhibition isn't complete and there is a measurable rebound in phospho-ERK at later time points [26] (**see Lito P et al, Cancer Cell 2012**). This provides the mechanistic basis for increased response to BRAF/MEK inhibitor combinations in melanoma. However future basic studies are awaited to define the differences in the inhibition of BRAF pathway for melanoma and CRC. All together, these studies hypothesize that the partial inhibition of the MAPK pathway might be the reason for the reduced sensitivity to vemurafenib by BRAF-mutated CRC.

Clinical Development

Phase I/II Trials

Main trials of anti-BRAF agents in mCRC summarized in Table 1. A pilot phase I trial explored the activity of vemurafenib single agent in 21 patients with BRAF-mutated mCRC. All but one received at least one prior chemotherapy line. Single-agent BRAF inhibitor showed unsatisfactory activity in this patient population. Only one patient obtained a partial response (PR), and seven, a stable disease (SD). As expected, the pharmacokinetic parameters (e.g. maximum concentration and area under the curve) after a single dose of vemurafenib did not differ from those observed in melanoma studies. [27]

Similar results from a phase II basket trial showed modest clinical activity of vemurafenib among heavily pretreated BRAF-mutated patients. In this study, 37 patients with CRC were treated with vemurafenib (n = 10) or vemurafenib plus cetuximab (n = 27), after the protocol had been amended. Only one patient in the vemurafenib and cetuximab cohort had a response (ORR 4%). Disease control rate (DCR) was 50% in patients treated with vemurafenib and 73% in patients treated with vemurafenib plus cetuximab. [28]

The combination of dabrafenib and trametinib was studied in a phase I/II trial enrolling 43 patients with BRAF-mutated mCRC. The combined BRAF and MEK inhibition produced higher ORR (12%) and DCR (68%) compared with those reported with a single-agent BRAF inhibitor. Overall, the median PFS was 3.5 months, but one patient obtained a long-lasting complete response (CR). The pharmacodynamic analysis showed a reduction in phosphorylated ERK levels, phosphorylated MAPK signaling components, and mTOR pathway targets, without significant changes in P-AKT levels, during the treatment, although the degree of MAPK signaling inhibition was inferior to the inhibition observed in patients treated for melanoma. [29]

Table 1

Summary of the main trials of anti-BRAF agents in mCRC

Trial	Phase	Treatment setting	Arms	Number of patients	Primary endpoint	ORR	DCR	PFS (months)	OS (months)
Kopetz et al. [26]	2	Predominantly pretreated patients	Vemurafenib	21	Pharmacokinetic parameters and ORR	4%	38%	2.1	7.7
Hyman et al. [27]	2	Heavily pretreated patients	Vemurafenib alone or vemurafenib plus cetuximab (after amendment)	37	8-week ORR	0% and 4%	50% and 73%	4.5 and 3.7	9.3 and 7.1
Corcoran et al. [28]	1–2	Predominantly pretreated patients	Dabrafenib and tramentinib	43	Safety	12%	68%	3.5	NR
Yaeger et al. [29]	1	After one or more chemotherapy lines	Vemurafenib and panitumumab	15	ORR	12%	NR	3.2	7.6
Van Geel et al. [30]	1b	Heavily pretreated patients	- Encorafenib and cetuximab - Encorafenib, cetuximab and alpelisib	54	RP2D	- 19.2% - 17.9%	- 76.9% - 92.8%	- 3.7 - 4.2	NR
Tabernero et al. [31]	2	Heavily pretreated patients	- Encorafenib, cetuximab and alpelisib - Encorafenib and cetuximab	102	PFS	- 27% - 22%	NR	- 5.4 - 4.2	- 15.2 - Not reached
Hong et al. [32]	1b	Heavily pretreated patients	Vemurafenib, irinotecan, and cetuximab	18	MTD of vemurafenib, safety	35%	88%	7.7	NR
Kopetz et al. [33]	2	Heavily pretreated patients	- Vemurafenib, irinotecan, and cetuximab - Irinotecan and cetuximab	106	PFS	- 16% - 4%	- 67% - 22%	- 4.4 - 2.0	NR
Corcoran et al. [34]	1–2	Predominantly pretreated patients	- Dabrafenib and panitumumab - Dabrafenib, trametinib, and panitumumab - Trametinib and panitumumab	142	Safety	- 10% - 21% - 10%	- 90% - 86% - 55%	- 3.5 - 4.2 - 2.6	- 13.2 - 9.1 - 8.2
Kopetz et al. [35]	3	After one or two chemotherapy lines	- Encorafenib, binimetinib, and cetuximab - Encorafenib and cetuximab - Cetuximab plus irinotecan or FOLFIRI (control group)	665	OS and ORR (triplet-therapy vs control group)	- 26% - 20% - 2%	- 68% - 74% - 31%	- 4.3 - 4.2 - 1.5	- 9.0 - 8.4 - 5.4

Abbreviations: DCR: disease control rate; MTD: maximum tolerated dose; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RP2D: recommended phase II dose.

A pilot trial explored the activity of vemurafenib combined with panitumumab in 15 patients with BRAFV600E-mutated CRC after the failure of prior standard treatments. The addition of panitumumab to the BRAF inhibitor was intended to overcome the resistance due to the feedback activation of EGFR. The proportion of patients who obtained a confirmed PR was 13%. Median PFS and OS were 3.2 and 7.6 months, respectively. Pharmacodynamic findings were similar to those reported in previous studies with BRAF inhibitors, confirming a considerable reduction in phosphorylated ERK and cyclin D1 during the treatment. [30]

A phase Ib trial evaluated the addition of the PI3K inhibitor alpelisib to encorafenib and cetuximab, in order to overcome the resistance to BRAF inhibitors. A total of 54 patients with BRAF-mutated mCRC were enrolled in two dose-escalation groups. Twenty-six patients received encorafenib plus cetuximab and 28 received encorafenib, cetuximab and alpelisib. Dose-limiting toxicities (DLTs) were experienced by 3 patients who received encorafenib/cetuximab (i.e. arthralgia, vomiting, and corrected QT interval prolongation) and 2 patients who received encorafenib/cetuximab/alpelisib (i.e. acute renal failure and interstitial pneumonitis). ORR was 19% in the encorafenib/cetuximab group and 18% in the encorafenib/cetuximab/alpelisib group, with a median PFS of 3.7 and 4.2 months, respectively. Within the treatment arms, the dose levels established as adequate for the phase II were 200 mg encorafenib daily and 300 mg alpelisib daily. [31] In the following phase II, a total of 102 patients were randomly assigned (1:1) to receive encorafenib/cetuximab or encorafenib/cetuximab/alpelisib. Median PFS was 5.4 months in the triplet-therapy group and 4.2 in the doublet-therapy group (HR 0.69; P = .064). Median OS was 15.2 in the triplet-therapy group and not reached in the doublet-therapy group. ORRs were 27% and 22%, respectively. [32]

The synergistic effect of EGFR and BRAF inhibition with cytotoxic chemotherapy was explored in a 3 + 3 phase Ib trial. Eighteen heavily pretreated patients with BRAFV600E-mutated mCRC received vemurafenib, irinotecan and cetuximab. Arthralgia and diarrhea were DLTs. The combination regimen was associated with promising clinical activity in terms of ORR (35%), DCR (88%), and PFS (7.7 months). Through the next-generation sequencing of the circulating cell-free DNA (cfDNA), potentially acquired resistance mechanisms have been identified, including MEK1, ARAF and GNAS mutations, and KRAS and BRAF amplifications. [33] In the phase II trial (SWOG S1406), the addition of vemurafenib to

cetuximab and irinotecan has been shown to improve PFS (4.4 vs 2.2 months; HR 0.42, 95% CI 0.26 to 0.66; P < .001) and ORR (16% vs 4%; P = .08). DCR was also significantly higher in the vemurafenib/cetuximab/irinotecan group compared with the cetuximab/irinotecan group (67% vs 22%). [34]

In a phase I/II trial, 142 patients with BRAFV600E-mutated mCRC received one of the following drug combinations: dabrafenib plus panitumumab, dabrafenib plus trametinib plus panitumumab (triplet-therapy group) or trametinib plus panitumumab, at first within dose-escalation cohorts, and then within expansion cohorts. Among patients treated with dabrafenib and panitumumab, DCR and ORR were 90% and 10%, respectively; median PFS was 3.5 months and median OS was 13.2 months. Among patients treated with the triplet therapy, DCR and ORR were 86% and 21%, respectively; median PFS was 4.2 months and median OS was 9.1 months. Among patients treated with trametinib and panitumumab, DCR was 55% and no PR or CR was reported; median PFS was 2.6 months and median OS was 8.2 months. During the treatment, a significant reduction in phosphorylated ERK levels was observed in the trametinib/panitumumab group and in the triplet-therapy group, but not in the dabrafenib/panitumumab group. A higher degree of inhibition of phosphorylated ERK was obtained with the triplet therapy (60%) compared with the other study treatments (23%-41%). Analyzing the cfDNA, a stronger decrease in BRAFV600E levels among patients with PR compared with those with SD or PD as best response (P = .004) was observed. In addition, acquired KRAS or NRAS mutations were detected in 48% of patients at the time of progression. [35]

Phase III Trials

BEACON CRC is the only randomized, multicentre phase III trial enrolling patients with BRAFV600E-mutated mCRC after the failure of one or two chemotherapy lines. A total of 665 patients were randomly assigned (1:1:1) to receive a triplet therapy (encorafenib, binimetinib, and cetuximab), a doublet therapy (encorafenib and cetuximab), or cetuximab plus irinotecan or FOLFIRI (control group). The distribution of primary tumor location was consistent with the literature; in particular, 50% to 56% of patients had right-sided primary tumors, 31% to 38% left-sided primary tumors, and 8% to 15% had both left- and right-sided primary tumors or unknown

location. The primary endpoints were met, with a median OS of 9.0 months in the triplet-therapy group and 5.4 months in the control group (HR 0.52; 95% CI, 0.39 to 0.70; $P < .001$), and an ORR of 26% and 2% ($P < .001$), respectively. Patients who received the doublet therapy achieved a median OS of 8.4 months and ORR of 20%, with a risk reduction of death of 40% compared with the control group (HR 0.60; 95% CI 0.45 to 0.79; $P < .001$). Likewise the PFS was longer in patients receiving triplet (4.3 months) or doublet therapy (4.2 months), compared with the control group (1.5 months), with HR values of 0.38 for the triplet-therapy group vs control group ($P < .001$) and 0.40 for the doublet-therapy group vs control group ($P < .001$). Overall, grade 3 to 4 adverse events (AEs) were observed in 58% of patients in the triplet-therapy group, 50% of patients in the doublet-therapy group, and 61% of patients in the control group. As expected, the MEK tyrosine kinase inhibitor (TKI) class toxicities were reported in patients treated with the triplet-therapy, but with a low incidence. No unexpected AE was observed in the treatment groups. According to this study, the chemotherapy-free targeted therapy led to the greatest benefit through the simultaneous inhibition of BRAF, MEK and EGFR. [36] According to the updated results from the BEACON CRC trial, triplet and doublet therapy confirmed their superiority over standard chemotherapy, showing a median OS of 9.3 for the triplet therapy and 9.3 months for the doublet therapy versus 5.9 months for the standard chemotherapy. In addition, a longer maintenance of quality of life was observed in patients treated with the chemotherapy-free regimens compared to those who received the standard chemotherapy, and there were no significant differences in the median time to deterioration in quality of life according to the two chemotherapy-free treatment groups. [37]

Ongoing Trials

The treatment of BRAFV600-mutated CRC is currently under investigation in several clinical trials specifically designed for this patient population. The phase II trial ANCHOR-CRC (NCT03693170) is evaluating the combination of encorafenib, binimetinib, and cetuximab in the first-line treatment of patients with BRAFV600E-mutated mCRC. In a phase Ib study (NCT02906059), patients with RAS- or BRAF-mutated mCRC are receiving irinotecan in combination with a selective Wee 1 inhibitor (AZD1775) in second-line treatment. The combination therapy of encorafenib and binimetinib with ribociclib is under investigation in a phase Ib/II trial (NCT01543698) enrolling patients with BRAFV600-mutated advanced cancer of various types including CRC. In a phase I trial (NCT01351103), patients with BRAF-mutated advanced cancers, including CRC, are treated with a specific PORCN inhibitor (LGK974) and anti-PD-1 PDR001 after the failure of standard treatments. The selective ERK1/2 inhibitor LY3214996 is currently under investigation in an interventional phase I trial (NCT02857270). In this trial, patients with advanced cancers, including BRAF-mutated CRC, receive LY3214996 alone or in combination with other agents. The randomized phase II study AIO-KRK-0116 (NCT04034459) compare FOLFOXIRI plus cetuximab with FOLFOXIRI plus bevacizumab as first-line treatment for patients with

BRAF-mutated mCRC. A phase I/II study (NCT04017650) is evaluating the combination of encorafenib and cetuximab with nivolumab in patients with MSS, BRAF-mutated mCRC.

Current Development Opportunities and Perspectives

As previously reported, among CRC patients, an association between BRAF-V600 mutations and dMMR/MSI-H phenotype has been observed. The simultaneous presence of the BRAF mutation and dMMR/MSI-H status has a better prognostic impact than the presence of the BRAF mutation in patients with MSS tumors. [13,14]. Several studies have explored the efficacy of immunotherapeutic agents in patients with dMMR/MSI-H CRC. Overall, these trials showed an ORR ranging from 33% to 52%, even in patients who had experienced PD after several lines of standard treatment. [38,39]. Some of these trials also included patients whose tumors harbored BRAF-V600 mutation [Table 2].

In the phase II trial KEYNOTE-164, pembrolizumab has shown a remarkable clinical activity in patients with chemo-refractory CRC. Among patients with BRAF-mutated tumor, ORR was 20% in second or further line treatment and 55% in third or further line treatment [38]. In the phase II trial CheckMate 142, patients with dMMR/MSI-H CRC received nivolumab alone or in combination with other agents (e.g., ipilimumab, anti-CD38 MoAb). Among 74 patients treated with nivolumab alone as second or further line treatment, 12 simultaneously had a mutation in BRAF. ORR was 41.4% in the BRAF and RAS WT group and 25.0% in the BRAF-mutated group, with a DCR for ≥12 weeks of 79.3% and 75%, respectively [40]. Additionally, the combination of nivolumab and low-dose ipilimumab was administered to patients with dMMR/MSI-H CRC who have undergone at least one previous line of chemotherapy. Nivolumab plus ipilimumab produced similar ORR and DCR across all molecular subtypes. More precisely, ORR and DCR were 55% and 79% in the BRAF-mutated subgroup compared with 55% and 77% in the BRAF and KRAS WT subgroup, and 57% and 84% in the KRAS-mutated subgroup [41]. Lastly, a cohort of 45 patients with dMMR/MSI-H CRC received the combination of nivolumab and low-dose ipilimumab in first-line treatment. Seventeen patients (38%) simultaneously had a mutation in BRAF and obtained an ORR of 71% and a DCR of 88%. [42]

Since the publication of the results of the phase III trial BEACON CRC, chemotherapy-free regimens have been considered an effective strategy for the treatment of advanced BRAF-mutated CRC who had progressed during one or two chemotherapy lines [36,37]. However, it is not yet clear whether the chemotherapy-free approach may also offer an advantage in the first-line treatment, where FOLFIRINOX plus bevacizumab currently remains the standard of treatment in fit patients [18].

Another key issue is the treatment choice that may offer the greatest benefit in patients with BRAF-mutated CRC and simultaneous dMMR/MSI-H phenotype. As previously reported, this patient subgroup is more likely to benefit from immunotherapeutic agents [38–41]. However, only a small number of patients with simultaneous mutations in BRAF have been included in the recently published immunotherapy studies. Therefore,

Table 2

Selection of the main trials of immunotherapy in dMMR/MSI-H CRC, including a proportion of BRAF-mutated patients

Trial	Phase	Treatment setting	Arms	Number of patients	Proportion of BRAF-mutated patients	Primary endpoint	ORR	DCR
KEYNOTE-164 [37]	2	- Cohort A: after two or more chemotherapy lines. - Cohort B: after one or more chemotherapy lines	Pembrolizumab	124	- A: 15% - B: 8%	ORR	- A: 55% - B: 20%	NR
CheckMate 142 [38]	2	After two or more chemotherapy lines	Nivolumab	74	16%	ORR	25%	Disease control for ≥12 weeks: 75%
CheckMate 142 [39]	2	After one or more chemotherapy lines	Nivolumab and low-dose ipilumumab	119	24%	ORR	55%	79%
CheckMate 142 [40]	2	First-line chemotherapy	Nivolumab and low-dose ipilumumab	45	38%	ORR	71%	88%

Abbreviations: DCR: disease control rate; dMMR: mismatch repair-deficient tumor; MSI-H: high microsatellite instability; NR: not reported; ORR: overall response rate.

the small number of BRAF-mutated patients within these studies precludes a precise estimate of the benefit from immunotherapeutic agents for this patient population.

In addition to a molecular selection of patients with BRAF-mutated CRC, a recent study (BRAF BeCool) has shown the opportunity to clinically select patients through a validated prognostic score. The score included several clinical factors with an independent prognostic impact for OS (i.e. ECOG performance status, CA19.9 value, LDH value, neutrophil/lymphocyte ratio, tumor grading, and the presence of liver, lung or lymph node metastases). A statistically significant longer OS was observed in the low-risk group (29.6 months) compared with the intermediate-risk group (15.5 months; $P < .001$) and high-risk group (6.6 months; $P < .001$). Similar results were obtained with the use of a simplified prognostic score that excluded blood test values. [43]

Given this high heterogeneity across BRAF-mutated patients, a molecularly and clinically based algorithm is crucial in order to offer the best choice of treatment for these patients, usually associated with poor prognosis.

Compliance with Ethical Standards

Conflict of interest the authors declare that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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