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Tumour Review

European expert panel consensus on the clinical management of *BRAF*^{V600E}-mutant metastatic colorectal cancer

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ABSTRACT

Metastatic colorectal cancer (mCRC) is a heterogenous disease caused by various genetic alterations. The *BRAF*^{V600E} mutation occurs in approximately 8–12% of patients and is characterised by an aggressive clinical course and poor prognosis. Here we review the current knowledge on *BRAF*^{V600E}-mutant mCRC and provide a series of consensus statements on its clinical management. The treatment landscape for *BRAF*^{V600E}-mutant mCRC has changed greatly due to the emergence of molecular targeted therapies (including BRAF inhibitors) and immune checkpoint inhibitors. A scientific literature search identified available data on molecular testing, treatments, and clinical monitoring of patients with *BRAF*^{V600E}-mutant mCRC. Consensus statements were discussed and developed by a European expert panel. This manuscript provides consensus management guidance for different clinical presentations of *BRAF*^{V600E}-mutant mCRC and makes recommendations regarding treatment sequencing choices. To guide appropriate clinical management and treatment decisions for mCRC patients, tumour tissue analysis for DNA mismatch repair/microsatellite status and, at a minimum, *KRAS*, *NRAS*, and *BRAF* mutational status is mandatory at the time of diagnosis. Finally, we discuss the rapidly evolving treatment landscape for *BRAF*^{V600E}-mutant mCRC and define priorities for the development of novel therapeutic strategies that are needed to improve patient outcomes.

Introduction

Globally, in 2019, colorectal cancer (CRC) resulted in the deaths of 1.09 million people, and there were 2.17 million new cases. [1] In Europe, CRC is the second most diagnosed cancer. Approximately 153,000 people are predicted to die from CRC in 2022 [2,3]. About 25% of patients with CRC are diagnosed at the metastatic stage, and 25% of patients with localised disease go on to develop metastases [4,5]. Although the prognosis of patients with metastatic CRC (mCRC) has improved greatly in recent years due to the introduction of more effective chemotherapies, targeted molecular therapies, and immunotherapies, overall survival (OS) remains largely poor (26.6% at 3 years and 15.4% at 5 years after diagnosis) [6].

Several factors may influence a patient's prognosis, including the presence of specific driver gene mutations. One key mutation that indicates a poor prognosis occurs in the *BRAF* gene, which encodes a key

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transducer in the mitogen-activated protein kinase (MAPK) signalling pathway that regulates both normal and cancer cell proliferation [7,8]. Based on the structure and function of the BRAF protein, *BRAF* mutations are subdivided into three groups: class 1 acts as RAS-independent monomers, with up to 700-fold greater kinase activity as compared with normal BRAF proteins; class 2 mainly acts as RAS-independent dimers, with an intermediate degree of kinase activity; whereas class 3 is RAS dependent, with a low kinase activity [9]. The occurrence of the most common *BRAF* mutation, *V600E* ($BRAF^{V600E}$; class 1 mutation) results in particularly poor prognoses for patients with mCRC [10]. Although fewer data are available, and clear correlations are yet to be defined, patients with class 2 and 3 non-$BRAF^{V600E}$ mutations appear to have more favourable outcomes [9,11–13]. Emerging data suggest that patients with class 2 mutations may suffer poorer prognosis than those with class 3 or *BRAF* wild-type mutations [11]. The *BRAF* mutation is found in the tumours of 8–12% of patients with mCRC [14].

The clinical management and treatment choices for patients with $BRAF^{V600E}$-mutant mCRC are particularly challenging. The findings from two large retrospective series of 255 European patients (CAPSTAN CRC) [10] and 395 patients from Italy [15] with $BRAF^{V600E}$-mutant mCRC highlight important and consistent characteristics of patients with this disease. Patients were a median of 66 years old when they were first treated; around two-thirds were diagnosed at stage IV; up to 65% had right-sided tumours; and metastases were most commonly in the liver (56–58%) followed by peritoneum, lymph nodes, and lung [10,15]. Further, the presence of *RAS/BRAF* mutations have been correlated with the occurrence of brain and lung metastases [16]. The aim of this European expert panel consensus paper is to review the most recent scientific data and provide consensus statements and recommendations on the molecular testing, treatment choices, and clinical monitoring of patients with $BRAF^{V600E}$-mutant mCRC.

Methods

Literature search

A literature search for original research as well as recent reviews and *meta*-analyses on the topics of molecular testing, monitoring, and treatment of patients with $BRAF^{V600E}$-mutant mCRC was conducted on PubMed. Congress materials on the same topics presented in 2021 and 2022 at the American Society of Clinical Oncology (ASCO) Annual Meetings, ASCO Gastrointestinal Cancers Symposia, European Society for Medical Oncology (ESMO) Congresses, and ESMO World Congresses on Gastrointestinal Cancer were also reviewed.

Expert panel and consensus procedures

An expert panel of nine European medical oncologists from Belgium, France, Italy, Germany, Spain, and UK met in person in June 2022; the experts were identified by the coordinating panellist (FC). Based on the meeting discussions, several consensus statements were drafted, and four clinical scenarios representative of patients diagnosed with $BRAF^{V600E}$-mutant mCRC were developed. In September 2022, panellists voted independently and anonymously on the online Vyva Sync platform (https://www.vyva.com/) on their level of agreement or disagreement with the consensus statements and on the appropriateness of different treatment choices for each clinical scenario. The level of agreement was rated from 1 (completely disagree) to 5 (completely agree); treatment appropriateness was rated from 1 (entirely inappropriate) to 5 (completely appropriate). Panellists also expressed their opinions on the priorities for clinical research on $BRAF^{V600E}$-mutant mCRC. Voting results were compiled by LiNK Health Group and discussed at a second virtual panel meeting in October 2022. Final consensus statements and treatment scenarios were approved by all panellists. The strength of evidence and agreement for each consensus statements were graded according to the definitions in Tables 1 and 2.

Table 1
Definitions for strength of evidence.

Evidence Level	Definition
1	Recommendation based on high-level evidence
2	Recommendation based on evidence and expert opinion
3	Recommendation based on lower-level evidence
4	Recommendation based on expert opinion

Table 2
Definitions for strength of agreement, where a score of 1 indicated complete disagreement, and 5 indicated complete agreement; scores of 5, 4, or 3 were regarded as agreement categories.

Agreement Level	Definition
A	100% of votes were in one agreement category (all panellists voted 5)
B	100% of votes in two contiguous agreement categories (all panellists voted 4 or 5)
C	100% of votes in three contiguous agreement categories (all panellists voted 3, 4, or 5)

Panel discussion on biomarker testing for mCRC

Molecular testing for certain gene alterations is currently considered mandatory for the clinical management of patients with mCRC. As established in the 2016 ESMO clinical practice guidelines for mCRC [14], the 2022 guidelines advise that, at the time of diagnosis, tumour tissue from patients with mCRC should be tested for *KRAS*, *NRAS,* and $BRAF^{V600E}$ mutations as well as for mismatch repair (MMR)/microsatellite status in order to select the most appropriate first-line and subsequent lines of therapy [17,18]. The $BRAF^{V600E}$ mutation is commonly mutually exclusive with either *KRAS* or *NRAS* mutations [10]. The $BRAF^{V600E}$ mutation may co-occur with deficient MMR (dMMR)/microsatellite instability-high (MSI-H) status [18,19]. Samples for molecular testing can be obtained during colonoscopy, surgical removal of the primary tumour, or biopsy of metastases prior to formalin fixation and paraffin embedding [17]. In the absence of tumour tissue, liquid biopsy (testing circulating tumour DNA [ctDNA] obtained from the peripheral blood) has been shown to be acceptable, either as an alternative or a complementary method to obtain results more quickly [20–22].

Commonly used molecular testing methods include Sanger sequencing, pyrosequencing, quantitative real-time polymerase chain reaction (qRT-PCR), high-resolution melting, next-generation sequencing (NGS), and immunohistochemistry (IHC); each has advantages and disadvantages [17,19]. IHC can evaluate MMR quickly and inexpensively, but it is not validated for mutated BRAF or RAS proteins. NGS allows the simultaneous evaluation of molecular alterations in multiple genes, but it is costly and requires experienced personnel [17,22]. Nevertheless, NGS is becoming the molecular testing method of choice over PCR [17,19,22,23]. ESMO recommends the use of NGS for advanced non-squamous non-small cell lung cancer, prostate cancer, ovarian cancer, and cholangiocarcinoma; in the case of CRC, ESMO recommends NGS as an alternative to PCR if no extra costs are associated [23]. The panel agrees on the need for expanding the use of NGS, where practicable, since it provides more comprehensive information on the mutational landscape of each patient, enabling the selection of the most appropriate treatments.

Consensus statements on biomarker testing for mCRC

1. The $BRAF^{V600E}$ mutation is the molecular driver of a subgroup (8–12%) of patients with mCRC and is associated with a particularly poor prognosis disease for which there are currently limited treatment options [Category 2B]

2. Molecular testing of patients with *BRAF*^{V600E}-mutant mCRC should be performed at diagnosis of metastatic disease to inform treatment sequence decisions and prevent delays in appropriate treatment [Category 2B]
3. At a minimum, patients with mCRC should be tested at diagnosis of metastatic disease for *KRAS/NRAS* (exons 2, 3, and 4) and *BRAF*^{V600E} mutations as well as for dMMR/MSI-H status [Category 2B]
4. The preferred method of mutational testing is genomic NGS or PCR if NGS is unavailable [Category 2A]
5. Due to the lack of adequate validation methods for mutated RAS and RAF proteins, IHC is recommended only for MMR status testing [Category 2C]
6. If no tissue is available, liquid biopsy to assess ctDNA is an adequate option for mutational testing of patients with mCRC [Category 2C]

Review of the current treatment landscape for BRAF^{V600E}*-Mutant mCRC*

The treatment landscape for patients with mCRC has evolved greatly over the last 2 decades. However, effective treatment options for patients with *BRAF*^{V600E} mutation remain limited.

Chemotherapy

For patients with mCRC, regardless of *KRAS/NRAS/BRAF* mutation status, doublet (FOLFIRI or FOLFOX/CAPOX) or triplet (FOLFOXIRI) chemotherapies in combination with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab are valid and effective first-line treatment options [18,24–26]. A *meta*-analysis of five randomised trials evaluating FOLFOXIRI + bevacizumab vs FOLFOX + bevacizumab (N = 1697) found no increased benefit for patients with *BRAF* mutations (n = 115) who were treated with first-line FOLFOXIRI + bevacizumab as compared with those treated with chemotherapy doublets + bevacizumab. OS was 13.6 months with FOLFOXIRI + bevacizumab vs 14.5 months with chemotherapy doublets + bevacizumab [27]. Analysis of real-world data in two separate studies indicated no additional benefit to first-line triplet chemotherapy compared with doublet chemotherapy for patients with *BRAF*-mutant mCRC, with the exception of patients with right-sided disease who did benefit from triplet chemotherapy [28,29]. Currently, ESMO clinical practice guidelines recommend doublet chemotherapy ± bevacizumab as first-line treatment in patients with *BRAF*^{V600E}-mutant mCRC and triplet chemotherapy ± bevacizumab as an additional option for those patients with right-sided *BRAF*^{V600E}-mutant tumours [18]. Future studies will be of value in examining these and other factors (such as Eastern Cooperative Oncology Group performance status [ECOG PS] [30]) in guiding treatment decisions in particular patient subsets.

Anti-vascular endothelial growth factor monoclonal antibodies

Data from a large US database show that VEGF inhibitors were a component of first-line therapy in the majority (57.2%) of patients with *BRAF*-mutant mCRC [31]. The benefit of adding the anti-VEGF bevacizumab to chemotherapy regimens has been reported in the overall population of patients with mCRC;[32,33] however, data specific to *BRAF* mutations are scarce, and the benefit of additional anti-VEGF therapy remains unclear in patients with *BRAF*^{V600E}-mutant mCRC. A pooled analysis of the TRIBE, TRIBE-2, VELOUR, and RAISE studies (n = 129) found bevacizumab and other anti-angiogenics to be efficacious in pretreated patients with *BRAF* mutations [34].

Anti-epidermal growth factor receptor monoclonal antibodies

ESMO clinical practice guidelines do not recommend combining anti-epidermal growth factor receptor (EGFR) antibodies with chemotherapy for patients with *BRAF*-mutant mCRC [18]. *BRAF*^{V600E} causes the constitutive activation of the MAPK pathway downstream of EGFR, thereby negating any effect of EGFR inhibitors; in addition, although EGFR is active in *BRAF*-mutant mCRC, the protein transmits its signal only after exposure to a BRAF inhibitor [35,36]. The CRYSTAL study demonstrated a non-significant trend towards improved benefit when FOLFIRI and cetuximab were combined for the treatment of *BRAF*-mutant mCRC (n = 59); for example, the median OS was 14.1 months with cetuximab vs 10.3 months without [37]. Similarly, the OPUS study, which included a small number of patients with *BRAF* mutations, reported a median OS of 20.7 months with FOLFOX4 + cetuximab (n = 6) and 4.4 months with FOLFOX4 alone (n = 5) [38]. A *meta*-analysis of 10 studies (n = 463) found that neither cetuximab nor panitumumab (as monotherapy or in combination with chemotherapy) increased the benefit in the first or second line for patients with *BRAF* mutations compared with chemotherapy ± bevacizumab or best supportive care [39]. Interestingly, a retrospective subgroup analysis of the FIRE-3 study found that outcomes in patients with *BRAF* mutations (n = 48) treated with FOLFIRI + cetuximab were similar to those treated with FOLFIRI + bevacizumab; the median OS was 13.7 months with bevacizumab and 12.3 months with cetuximab; the median progression-free survival (PFS) was 6.6 months for both [40]. The phase 2 FIRE-4.5 study (n = 108), which specifically evaluated the efficacy and safety of first-line FOLFOXIRI + bevacizumab vs FOLFOXIRI + cetuximab in *BRAF*-mutant mCRC, found FOLFOXIRI + bevacizumab to be more favourable than FOLFOXIRI + cetuximab for patients with *BRAF*^{V600E}-mutant mCRC. Although the objective response rate (ORR) was similar between the two arms (60.0% with bevacizumab vs 49.2% with cetuximab), the median PFS was significantly longer with bevacizumab than cetuximab (10.1 vs 6.3 months). The authors also reported that patients with right-sided primary tumours benefitted more from FOLFOXIRI + bevacizumab treatment [41].

Immune checkpoint inhibitors

BRAF mutations are frequent in the CMS1, which is strongly associated with tumours characterised by microsatellite instability (MSI) [42]. Immune checkpoint inhibitors (pembrolizumab, ipilimumab + nivolumab) are the treatment of choice for patients with *BRAF*-mutant MSI-H mCRC [43,44]. The available trial data on immune checkpoint inhibitors are promising, although scarce regarding the *BRAF*-mutant population. The KEYNOTE-177 study evaluated pembrolizumab vs chemotherapy in untreated patients with MSI-H/dMMR mCRC. Among patients with *BRAF* mutations (n = 81), there was a trend towards improved OS with pembrolizumab vs chemotherapy; after a median follow-up of 44.5 months, the median OS with pembrolizumab had not been reached (95% confidence interval [CI]: 26.4–not reached), and the median OS with chemotherapy was 45.2 months (95% CI: 21.0–not reached; hazard ratio [95% CI]: 0.72 [0.35–1.47]) (this study had a notably high crossover rate of 60% from chemotherapy to pembrolizumab following disease progression, which likely resulted in the improved OS of the chemotherapy group) [45]. KEYNOTE-164 evaluated pembrolizumab in patients with MSI-H/dMMR mCRC previously treated with ≥2 (cohort A) or ≥1 (cohort B) prior lines of therapy. Among patients with *BRAF*-mutant mCRC, the ORR was 55% in cohort A (n = 9) and 20% in cohort B (n = 5) [46]. The phase 2 non-randomised CheckMate-142 study evaluated ipilimumab + nivolumab; among previously treated patients with *BRAF*-mutant MSI-H/dMMR mCRC (n = 30), the investigator-assessed ORR was 70% after a median follow-up of 50.9 months [47]. Based on the data from CheckMate-142, ipilimumab + nivolumab were approved in Europe for second-line treatment of MSI-H/dMMR mCRC following progression on chemotherapy [48,49]. Notably, in the US, nivolumab is also approved for use as monotherapy in the same patient population; authors reported an ORR of 25% in patients with *BRAF*-mutant tumours (n = 12) [50,51]. In the absence of a head-to-head comparison, the authors noted a general trend of higher response rates in the overall MSI-H/dMMR mCRC population with ipilimumab + nivolumab compared with nivolumab alone [47].

BRAF inhibitors

As a monotherapy, BRAF inhibitors (encorafenib, dabrafenib, and vemurafenib) have shown limited treatment effects [52–54]. BRAF inhibition alone suppresses ERK-mediated negative feedback regulation of EGFR, leading to EGFR activation and consequent reactivation of the MAPK pathway; this paradoxical activation is prevented by coadministration of an EGFR inhibitor [35]. Although the EGFR inhibitor cetuximab was not beneficial as a monotherapy or in combination with only chemotherapy, it has been shown to be effective in combination with the BRAF inhibitor encorafenib [37,39,55]. The phase 3 BEACON CRC trial compared encorafenib + cetuximab (±binimetinib) with cetuximab + chemotherapy in 665 patients with *BRAF*^{V600E}-mutant mCRC following progression on 1–2 prior regimens [55]. Median OS was 9.3 months with second- or third-line encorafenib + cetuximab (n = 220) vs 5.9 months with control (cetuximab + irinotecan/FOLFIRI; n = 221) [55]. As a result, ESMO clinical practice guidelines state encorafenib + cetuximab as the best options for second- and third-line treatment of patients with *BRAF*-mutant mCRC [18]. We recommend that, upon progression following any first-line treatment, patients be treated with encorafenib + cetuximab as early as possible (ie, in second line rather than later in third line). The BEACON study also investigated encorafenib + cetuximab in combination with the MEK inhibitor binimetinib. Further inhibition of the MAPK pathway with MEK inhibitors may result in a greater clinical benefit; however, adaptive feedback signals may hamper the increased efficacy of such combinations [56]. Encorafenib + cetuximab + binimetinib (n = 224) resulted in an OS of 9.3 months, similar to that with encorafenib + cetuximab without binimetinib; additionally, investigators observed an increase in specific toxicities related to MEK inhibition (eg, dermatological, gastrointestinal, and ocular adverse effects) [55]. There were no clear clinical differences that indicate which patient subgroups may benefit from the addition of binimetinib to encorafenib + cetuximab in second line [55]. This same triple-targeted regimen has now been examined in the first-line setting: the single-arm ANCHOR CRC study evaluated encorafenib + cetuximab + binimetinib as first-line treatment for *BRAF*-mutant mCRC (n = 95) [57,58]. The primary endpoint of locally assessed confirmed ORR (47.4%) was met, while median OS was 18.3 months, median PFS was 5.8 months, and no unexpected toxicities were observed [57,58].

Combining BRAF and EGFR inhibitors with chemotherapy is also of interest. The phase 3 BREAKWATER study evaluated encorafenib + cetuximab ± chemotherapy (mFOLFOX6 [modified FOLFOX-6: folinic acid + 5-fluorouracil (5-FU) + oxaliplatin]) vs chemotherapy (mFOLFOX6, FOLFIRI, or CAPOX [capecitabine + oxaliplatin]) ± bevacizumab for the first-line treatment of *BRAF*^{V600E}-mutant mCRC [59]. The safety lead-in analysis for this study demonstrated promising preliminary antitumour activity in the first and second line; ORRs ranged from 50% to 68%, and the median PFS was approximately 10 months with both first- and second-line encorafenib + cetuximab + mFOLFOX6 (the median PFS with encorafenib + cetuximab + FOLFIRI had not been reached) [60]. The phase 2 SWOG 1406 study evaluated vemurafenib + irinotecan + cetuximab (VIC regimen; n = 50) vs irinotecan + cetuximab (n = 50) in previously treated patients with *BRAF*^{V600E}-mutant mCRC. Investigators reported improved PFS (4.2 vs 2.0 months) and ORR (17% vs 4%) [61]. Another phase 2 study, IMPROVEMENT, evaluated vemurafenib + cetuximab + FOLFIRI in untreated and previously treated patients (n = 21); the median OS and PFS were 15.4 and 9.7 months, respectively; the ORR was 81% [62].

Other systemic treatments

In later treatment lines, patients may receive regorafenib (multikinase inhibitor) or trifluridine/tipiracil (thymidine analogue + thymidine phosphorylase inhibitor). However, there are no available data to evaluate these drugs in patient subgroups with *BRAF*-mutant mCRC [44,63]. ESMO clinical practice guidelines recommend regorafenib and trifluridine/tipiracil for patients who have previously received fluoropyrimidines, oxaliplatin, irinotecan, and biologics, or experienced disease progression following treatment with oxaliplatin and irinotecan [18].

Surgical resection

Surgical resection may be considered for patients with *BRAF*-mutant mCRC; a subset may derive survival benefit from metastasectomy [64]. The prognosis is poor and may preclude patients from surgery with a curative intent. Although surgery for liver metastases is a viable option, recurrence after surgery is more frequent and more severe in patients with *BRAF* mutations than in those without [65]. Depending on the characteristics of the patients and their tumours, surgery with a curative intent or ablative therapy may be considered for those who have a low tumour burden or good treatment response. We recommend that each case be evaluated at a multidisciplinary team meeting, keeping in mind the poor prognosis of the *BRAF* mutation (and the potential consequences of stopping systemic treatment in order to perform surgery). A multi-institutional examination of registry records of 240 patients with *BRAF*-mutant colorectal liver metastases found that, in patients with *BRAF*^{V600E}-mutant disease, there was no statistical difference in OS between those with upfront resectable vs converted (by preliminary chemotherapy) disease [66]. These data suggest that conversion chemotherapy followed by surgery is a viable strategy for patients with *BRAF*^{V600E}-mutant colorectal liver metastases. The same study found that patients with the *BRAF*^{V600E}-mutation and extra-hepatic metastases had extremely poor survival outcomes, such that surgery is unlikely to provide a clinically significant benefit in that group [66]. ESMO clinical practice guidelines do not recommend excluding patients with *BRAF*-mutant mCRC from potentially curative surgical procedures [18].

Clinical monitoring of patients with BRAF^{V600E}*-Mutant mCRC*

Due to the aggressive nature of *BRAF*^{V600E}-mutant mCRC, patients with this disease require more frequent monitoring than patients without *BRAF*^{V600E} mutations. Patients should be examined at least every 2 months to evaluate treatment response. This will also provide an opportunity to review treatment goals and, if necessary, discuss other treatment options [67]. Physical examinations, radiological scans, and blood tests are standard [24]. ESMO clinical practice guidelines recommend radiological monitoring and the measurement of carcinoembryonic antigen levels [18]. Treatment monitoring using ctDNA is an evolving field [68]. Currently, we do not recommend using liquid biopsy for monitoring.

It should be noted that radiological imaging to monitor treatment response or disease progression may prove difficult due to the lower accuracy of computed tomography (CT) and positron emission tomography (PET) CT in detecting peritoneal metastases. Although a recently published report found diffusion-weighted magnetic resonance imaging to be highly sensitive and specific for the detection of peritoneal metastases, its use may not be routine [69,70].

Panel discussion on the clinical management of BRAF^{V600E}*-Mutant mCRC*

Typical cases of *BRAF*^{V600E}-mutant mCRC predominantly involve older, female patients with right-sided (proximal) MSI tumours with poorly differentiated mucinous histology. Nevertheless, patients with other clinical characteristics, including younger age of presentation, are also diagnosed with *BRAF*^{V600E}-mutant mCRC. Diagnoses are usually made in an advanced stage; metastases tend to occur in the liver, peritoneum, lymph nodes, and lungs [10,11,71]. In CAPSTAN CRC, 52.5% of patients went on to receive any second-line therapy, and 30.2% received third-line treatment, underlining the aggressiveness of this disease [10]. Four hypothetical clinical scenarios representative of patients diagnosed with *BRAF*^{V600E}-mutant mCRC are outlined in Table 3.

Table 3
Hypothetical clinical scenarios involving patients with *BRAF*^{V600E}-mutant mCRC.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Age (years)	75	72	32	40
Sex	Male	Female	Female	Female
ECOG PS	2	2	1	2
Primary tumour	Right-sided tumour	Right-sided tumour removed 6 months ago; no adjuvant therapy	Left-sided tumour; asymptomatic	Right-sided tumour; technically resectable (T3N2)
Metastases	Small, unresectable liver metastases	Unresectable liver metastases	Liver metastases initially unresectable; may become resectable with treatment	Peritoneal metastases; potentially resectable
Biomarkers	*BRAF*^{V600E}, *KRAS/NRAS* wt, MSS	*BRAF*^{V600E}, *KRAS/RAS* wt, MSI-H	*BRAF*^{V600E}, *KRAS/NRAS* wt, MSS	*BRAF*^{V600E}, *KRAS/RAS* wt, MSI-H
Comorbidities	Cardiac and renal impairment	None	None	None

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PS, performance status; wt, wild-type.

For each scenario, consensus treatment recommendations are shown as heatmaps in Fig. 1; individual treatment preferences of each consensus panel members are also included to demonstrate the variable and complex treatment decisions surrounding *BRAF*^{V600E}-mutant mCRC. Recommendations are based on clinical evidence and expert opinion; however, certain treatments (eg, trifluridine/tipiracil + bevacizumab, ipilimumab for mCRC, regorafenib) may not be currently reimbursed in some European countries. For all these complex clinical scenarios, enrolment in relevant clinical trials may be a valuable treatment approach and should be considered alongside the presented therapeutic options.

Scenario 1: Older patient with a right-sided tumour and comorbidities

For this patient (Table 3, Fig. 1), the consensus recommendation was for doublet chemotherapy + bevacizumab in the first line. Although there is literature to support a choice of triplet over doublet chemotherapy for patients with a *BRAF*-mutant right-sided tumour [18,28,29], due to this patient's age, high ECOG PS score of 2, and potential comorbidities, FOLFOXIRI is not recommended. Upon progression, the patient should receive encorafenib + cetuximab (preferred, and based upon the BEACON data [55]) or doublet chemotherapy + bevacizumab (ie, FOLFIRI, if FOLFOX was given in the first line and vice versa). Based on the patient's history, they are unlikely to receive more than one or two lines of treatment; however, assuming that the patient's condition does not deteriorate with time, trifluridine/tipiracil ± bevacizumab and regorafenib are appropriate options for third- and fourth-line treatment, respectively. When making treatment decisions, one must also consider the reasons behind the patient's ECOG PS of 2. If the reasons are fast disease progression and extensive metastases, then the patient may improve following first-line chemotherapy. Otherwise, the treatment regimen should be tailored to the patient's comorbidities.

Scenario 2: Patient with MSI-H disease and unresectable metastases

Based on this patient's MSI-H status (Table 3, Fig. 1), we recommend first-line treatment with immune checkpoint inhibitors, preferably pembrolizumab, in accordance with the findings from the KEYNOTE-177 phase 3 study [45], followed by encorafenib + cetuximab in the second line. The recommendation for second-line therapy aligns with the current ESMO guidelines for mCRC [18], drawing on data from the BEACON trial that indicate a survival benefit from encorafenib + cetuximab versus chemotherapy [18,55]. A small proportion (<10%) of patients in BEACON were MSI-H, but initial treatment with immunotherapy was not examined as part of the study. Nevertheless, considering the general scarcity of data in *BRAF*-mutant/MSI-H patients, these are the strongest available data on which to base our recommendations in conjunction with clinical judgement. We recommend doublet chemotherapy + bevacizumab as appropriate in the third and fourth lines (eg, FOLFOX + bevacizumab in the third line and FOLFIRI + bevacizumab in the fourth line, or the reverse sequence), while trifluridine/tipiracil ± bevacizumab is also a valid third-line option with supportive evidence from the SUNLIGHT study [72]. Regorafenib may be considered in the fifth and sixth line, respectively, if the patient's condition allows.

Scenario 3: Younger patient with an asymptomatic primary tumour, potentially resectable metastases, and good performance status

In this young patient with no comorbidities, an asymptomatic primary tumour, and a limited number of metastases that are confined to the liver and potentially resectable, resection of metastases may be attempted at an opportune time following or during systemic treatment. ESMO clinical practice guidelines do not recommend resecting asymptomatic primary tumours in patients with unresectable metastatic disease [18]. For systemic therapy, we recommend triplet (preferred) or doublet chemotherapy + bevacizumab in the first line and encorafenib + cetuximab in the second line. As can be seen from the panel voting in Fig. 1, the decision between selecting first-line triplet over doublet chemotherapy is not a straightforward one. In this case, the slight bias towards triplet chemotherapy is based on relative youth and good performance status in this scenario balanced against a left-sided tumour, which may benefit more from doublet chemotherapy [28]. Trifluridine/tipiracil ± bevacizumab [72] and regorafenib are appropriate options for third- and fourth-line treatment, respectively.

Scenario 4: Younger patient with MSI-H disease, a resectable primary tumour, and potentially resectable peritoneal metastases

Immune checkpoint inhibitors, preferably pembrolizumab according to KEYNOTE-177 trial results, should be the first line of treatment for this patient [45]. As an alternative to pembrolizumab, nivolumab plus ipilimumab might be used according to the results of the first-line therapy cohort from CHECKMATE-142, where the response rate in patients with MSI-H and *BRAF*-mutated disease was 82% [47,73]. The primary and metastatic tumours may be resected at an opportune time if they become resectable following or during treatment, as this will impact on OS. Encorafenib + cetuximab should be given in the second line and doublet chemotherapy + bevacizumab in the third line. Rifluridine/tipiracil ± bevacizumab [72] and regorafenib may be considered in the fourth and fifth line, respectively.

Consensus statements on the clinical management of BRAF^{V600E}*-Mutant mCRC*

1. The preferred first-line therapy for patients with MSI-H *BRAF*^{V600E}-mutant mCRC are immune checkpoint inhibitors, preferably pembrolizumab (or ipilimumab + nivolumab, if available) [Category 1A]
2. The preferred first-line therapy for patients with microsatellite stable (MSS) *BRAF*^{V600E}-mutant mCRC is doublet chemotherapy ± bevacizumab, or triplet chemotherapy ± bevacizumab only in selected cases (such as younger patients, those with good performance status and/or potentially resectable disease with sufficient tumour shrinkage, and/or those with right-sided tumours) [Category 2B]

Scale: Entirely inappropriate | 1 | 2 | 3 | 4 | 5 | Completely appropriate

Clinical scenario 1 (Older patient with a right-sided tumour and comorbidities): Consensus treatment recommendations

Treatment line	FOLFOX	FOLFIRI	FOLFOXIRI	Bevacizumab	Encorafenib + cetuximab	Pembrolizumab	Ipilimumab (if available)	Nivolumab	Regorafenib	Trifluridine/ tipiracil	Intent to resect metastases	Best supportive care
First line	3.9	3.6	1.0	3.7	1.6	1.0	1.0	1.0	1.0	1.1	1.3	2.6
Second line	2.6	2.4	1.0	2.0	4.1	1.0	1.0	1.0	1.2	1.7	1.2	2.9
Third line	1.6	1.9	1.0	1.8	3.4	1.1	1.1	1.1	3.0	3.8	1.0	3.6
Fourth line	1.3	1.3	1.0	1.6	2.3	1.0	1.0	1.0	3.6	3.7	1.0	4.2

Clinical scenario 1 (Older patient with a right-sided tumour and comorbidities): Individual panellist treatment recommendations

Treatment line	FOLFOX			FOLFIRI			FOLFOXIRI			Bevacizumab			Encorafenib + cetuximab			Pembrolizumab			Ipilimumab (if available)			Nivolumab			Regorafenib			Trifluridine/ tipiracil			Intent to resect metastases			Best supportive care		
First line	3	5	2	2	4	4	1	1	1	5	5	2	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	1	3
	4	4	4	4	2	4	1	1	1	3	3	3	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5
	5	4	4	5	4	3	1	1	1	5	3	4	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	4	1	1	2	3	2
Second line	1	4	3	1	5	3	1	1	1	1	5	1	5	5	4	1	1	1	1	1	1	1	1	1	1	3	1	1	3	1	1	1	1	5	1	3
	1	4	4	1	2	4	1	1	1	1	3	2	5	1	5	1	1	1	1	1	1	1	1	1	1	1	1	3	1	2	1	1	1	1	3	5
	1	4	1	1	4	1	1	1	1	1	3	1	5	3	4	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	3	1	1	2	4	2
Third line	2	2	1	3	2	1	1	1	1	5	1	1	1	5	3	1	1	1	1	1	1	1	1	1	3	4	1	4	4	1	1	1	1	5	1	3
	1	1	3	1	1	3	1	1	1	1	1	1	3	5	5	1	1	1	1	1	1	1	1	1	3	4	3	5	4	4	1	1	1	1	5	5
	1	2	1	1	2	3	1	1	1	1	2	3	1	5	3	1	1	2	1	1	2	1	1	2	5	1	3	5	4	3	1	1	1	4	5	3
Fourth line	1	2	1	1	2	1	1	1	1	4	1	1	1	3	1	1	1	1	1	1	1	1	1	1	2	5	2	2	5	2	1	1	1	5	4	5
	1	1	2	1	1	2	1	1	1	1	1	1	1	5	3	1	1	1	1	1	1	1	1	1	5	5	3	3	5	4	1	1	1	1	5	5
	1	2	1	1	2	1	1	1	1	1	1	3	1	5	1	1	1	1	1	1	1	1	1	1	5	2	3	5	4	3	1	1	1	4	5	4

Clinical scenario 2 (Patient with MSI-H disease and unresectable metastases): Consensus treatment recommendations

Treatment line	FOLFOX	FOLFIRI	FOLFOXIRI	Bevacizumab	Encorafenib + cetuximab	Pembrolizumab	Ipilimumab (if available)	Nivolumab	Regorafenib	Trifluridine/ tipiracil	Intent to resect metastases	Best supportive care
First line	1.7	1.7	1.1	1.6	1.1	5.0	3.2	3.4	1.0	1.0	1.4	1.2
Second line	2.6	2.6	1.3	2.1	4.7	1.9	2.2	2.1	1.0	1.0	1.4	1.2
Third line	3.7	3.4	1.6	3.4	3.2	1.9	2.3	2.1	2.0	2.7	1.1	1.6
Fourth line	1.8	2.0	1.0	2.2	1.8	1.3	2.1	1.9	3.2	2.9	1.1	3.0

Clinical scenario 2 (Patient with MSI-H disease and unresectable metastases): Individual panellist treatment recommendations

Treatment line	FOLFOX			FOLFIRI			FOLFOXIRI			Bevacizumab			Encorafenib + cetuximab			Pembrolizumab			Ipilimumab (if available)			Nivolumab			Regorafenib			Trifluridine/ tipiracil			Intent to resect metastases			Best supportive care		
First line	1	1	3	1	1	3	1	1	1	1	1	2	1	1	1	5	5	5	5	3	3	5	3	3	1	1	1	1	1	1	1	1	1	1	1	2
	3	1	1	3	1	1	1	1	1	3	1	1	1	1	1	5	5	5	4	1	3	4	1	5	1	1	1	1	1	1	1	1	1	1	1	2
	1	2	2	1	2	2	1	2	1	1	2	2	1	2	1	5	5	5	3	3	4	3	3	4	1	1	1	1	1	1	5	1	1	1	1	1
Second line	1	1	3	1	1	3	1	1	1	1	1	1	5	5	5	1	1	3	1	1	2	1	1	2	1	1	1	1	1	1	1	1	1	1	1	2
	4	3	4	4	3	4	1	1	1	4	1	4	5	5	4	4	1	4	4	1	5	4	1	4	1	1	1	1	1	1	1	1	1	1	1	2
	3	2	2	3	2	2	3	2	1	3	2	2	5	4	4	1	1	1	1	1	4	1	1	4	1	1	1	1	1	1	5	1	1	1	1	1
Third line	3	5	2	3	5	2	1	5	1	4	5	1	1	5	5	1	1	1	1	1	1	1	1	1	1	1	1	4	1	2	1	1	1	1	1	3
	5	2	3	5	2	3	1	1	1	5	2	3	5	5	3	3	1	3	3	5	5	3	5	3	3	4	3	3	4	5	1	1	1	1	1	2
	5	4	4	5	3	3	2	1	1	5	2	4	3	1	1	5	1	1	1	1	3	1	1	3	1	2	2	1	2	2	2	1	1	1	1	3
Fourth line	1	5	1	1	5	1	1	1	1	4	5	1	1	1	1	1	1	1	1	1	1	1	1	1	4	1	1	1	1	3	1	1	1	5	1	4
	1	1	2	1	1	2	1	1	1	1	1	2	3	5	2	2	1	2	2	5	5	2	5	3	5	4	4	5	4	2	1	1	1	1	5	2
	1	3	1	1	3	3	1	1	1	1	2	3	1	1	1	1	2	1	1	2	1	1	2	1	5	2	3	5	2	3	2	1	1	4	1	4

Fig. 1. Heatmaps of consensus and individual treatment recommendations for clinical scenarios in Table 1. Panellists voted on the appropriateness of each treatment on a scale of 1 (entirely inappropriate) to 5 (completely appropriate). Mean and individual appropriateness values for each treatment at each treatment line are shown for consensus and individual recommendations, respectively. Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high.

3. Upon progression following first-line treatment, patients with *BRAF*^{V600E}-mutant mCRC should be treated with encorafenib + cetuximab as soon as possible [Category 1A]
4. Radiological monitoring of patients under treatment for *BRAF*^{V600E}-mutant mCRC should be performed at least every 2 months to avoid unnecessary delays in detecting disease progression and the need for changing therapy [Category 2B]

Future research priorities

There have been substantial and meaningful advances in the treatment of *BRAF*^{V600E}-mutant mCRC in the last few years. Nevertheless, the rate and duration of response in patients with *BRAF*^{V600E}-mutant mCRC remains low in comparison with other mCRC subpopulations [74]. Data from ongoing trials will be pivotal in informing the rational use of targeted and combined therapies (Table 4).

Multiple trials are evaluating the combination of BRAF inhibitors with immune checkpoint inhibitors. The phase 2 SEAMARK study evaluated encorafenib + cetuximab + pembrolizumab vs pembrolizumab for the first-line treatment of *BRAF*^{V600E}-mutant MSI-H/dMMR mCRC [75]. A single-arm phase 1/2 study (NCT04017650) evaluating encorafenib + cetuximab + nivolumab in previously treated patients (n = 26) reported a median OS of 11.4 months and ORR of 45%; as a follow-up, the single-arm phase 2 SWOG 2107 study further evaluated encorafenib + cetuximab + nivolumab in previously treated patients with *BRAF*^{V600E}-mutant MSS mCRC [76–78]. The BRAF inhibitor dabrafenib + MEK inhibitor trametinib have shown a modest activity in phase 1/2 studies [56,79]. More recently, a single-arm phase 2 study

Clinical scenario 3 (Younger patient with asymptomatic primary tumour, potentially resectable metastases, and good ECOG PS): Consensus treatment recommendations

Treatment line	FOLFOX	FOLFIRI	FOLFOXIRI	Bevacizumab	Encorafenib + cetuximab	Pembrolizumab	Ipilimumab (if available)	Nivolumab	Regorafenib	Trifluridine/ tipiracil	Intent to resect metastases	Best supportive care
First line	3.4	3.1	4.2	3.7	1.6	1.0	1.0	1.0	1.0	1.0	3.7	1.1
Second line	2.8	2.8	1.8	2.7	4.9	1.0	1.0	1.0	1.0	1.0	3.8	1.2
Third line	2.3	2.4	1.6	2.0	3.2	1.0	1.0	1.0	2.9	3.1	2.0	2.0
Fourth line	1.7	1.8	1.6	1.9	1.9	1.1	1.0	1.0	3.8	4.0	1.8	3.1

Clinical scenario 3 (Younger patient with asymptomatic primary tumour, potentially resectable metastases, and good ECOG PS): Individual panellist treatment recommendations

Treatment line	FOLFOX			FOLFIRI			FOLFOXIRI			Bevacizumab			Encorafenib + cetuximab			Pembrolizumab			Ipilimumab (if available)			Nivolumab			Regorafenib			Trifluridine/ tipiracil			Intent to resect metastases			Best supportive care		
First line	5	3	4	4	3	4	5	5	5	1	5	4	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	5	1	1	1	1
	5	4	1	4	4	1	5	5	1	5	5	1	2	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	2	1	1	2
	3	2	4	3	2	3	5	2	5	5	2	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	4	5	1	1	1
Second line	1	3	3	1	3	3	1	1	2	1	3	2	5	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	4	5	1	1	1	1
	3	4	3	3	4	3	1	1	2	3	5	2	5	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	5	1	1	3
	5	2	1	5	2	1	5	2	1	5	2	1	5	4	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	5	4	4	1	1	1
Third line	3	4	2	3	4	2	2	1	2	5	1	2	1	5	4	1	1	1	1	1	1	1	1	1	2	1	1	2	1	2	2	1	1	2	1	1
	1	2	3	1	2	3	1	1	2	1	1	2	3	5	5	1	1	1	1	1	1	1	1	1	5	4	5	5	4	4	1	2	5	1	1	4
	1	3	2	1	3	3	1	3	1	1	2	3	3	1	2	1	1	1	1	1	1	1	1	1	5	1	2	5	1	4	2	3	1	4	3	1
Fourth line	2	1	1	3	1	1	1	1	1	3	1	1	1	1	3	1	1	1	1	1	1	1	1	1	4	4	2	4	4	3	1	1	1	5	3	2
	1	1	4	1	1	4	1	1	4	1	1	4	1	5	3	1	1	1	1	1	1	1	1	1	5	4	4	5	4	5	1	2	5	1	2	5
	1	3	1	1	3	1	1	3	1	1	4	1	1	1	1	1	2	1	1	1	1	1	1	1	5	2	4	5	2	4	2	2	1	4	3	3

Clinical scenario 4 (Younger patient with MSI-H disease, a resectable primary tumour, and potentially resectable peritoneal metastases): Consensus treatment recommendations

Treatment line	FOLFOX	FOLFIRI	FOLFOXIRI	Bevacizumab	Encorafenib + cetuximab	Pembrolizumab	Ipilimumab (if available)	Nivolumab	Regorafenib	Trifluridine/ tipiracil	Intent to resect metastases	Best supportive care
First line	1.9	1.9	1.8	2.3	1.2	4.7	3.7	3.9	1.0	1.0	3.3	1.0
Second line	2.4	2.4	2.3	3.1	4.7	2.0	2.6	2.4	1.0	1.0	3.1	1.0
Third line	3.8	3.7	1.8	3.4	3.2	1.6	2.6	2.3	2.1	2.2	1.7	2.0
Fourth line	2.2	2.4	1.1	1.7	1.8	1.4	2.0	1.8	3.2	3.4	1.3	2.6

Clinical scenario 4 (Younger patient with MSI-H disease, a resectable primary tumour, and potentially resectable peritoneal metastases): Individual panellist treatment recommendations

Treatment line	FOLFOX			FOLFIRI			FOLFOXIRI			Bevacizumab			Encorafenib + cetuximab			Pembrolizumab			Ipilimumab (if available)			Nivolumab			Regorafenib			Trifluridine/ tipiracil			Intent to resect metastases			Best supportive care		
First line	1	1	3	1	1	3	1	1	3	1	1	3	1	1	1	5	5	5	5	4	4	5	4	4	1	1	1	1	1	1	5	5	1	1	1	1
	5	1	1	5	1	1	5	1	1	5	5	1	3	1	1	5	5	4	5	1	3	5	1	5	1	1	1	1	1	1	4	3	2	1	1	1
	2	2	1	2	2	1	2	1	1	2	2	1	1	1	1	5	3	5	3	4	4	3	4	4	1	1	1	1	1	1	5	1	4	1	1	1
Second line	1	1	3	1	1	3	1	5	3	1	5	3	5	5	4	1	1	3	1	3	3	1	3	3	1	1	1	1	1	1	5	5	1	1	1	1
	5	4	3	5	4	3	3	1	4	5	5	4	5	5	4	5	1	4	5	1	5	5	1	4	1	1	1	1	1	1	2	3	3	1	1	1
	1	2	2	1	2	2	1	1	2	1	2	2	5	4	5	1	1	1	1	1	3	1	1	3	1	1	1	1	1	1	5	1	3	1	1	1
Third line	4	5	2	4	5	2	3	3	1	4	5	2	1	5	4	1	1	2	1	1	2	1	1	2	1	2	1	1	2	2	4	1	1	2	1	1
	3	3	4	3	3	4	1	1	3	3	3	3	5	5	3	3	1	3	3	5	5	3	5	3	3	4	5	3	4	5	1	1	3	1	1	4
	5	4	4	5	4	3	1	2	1	5	2	4	1	1	4	1	1	1	1	1	4	1	1	4	1	1	1	1	1	1	2	1	1	3	4	1
Fourth line	4	5	1	4	5	1	2	1	1	3	1	1	1	1	2	1	1	1	1	1	1	1	1	1	4	1	1	4	1	2	1	1	1	5	1	1
	1	1	2	1	1	2	1	1	1	1	1	2	2	5	2	2	1	2	2	5	5	2	5	3	5	4	5	5	4	5	1	1	3	1	2	5
	1	3	2	1	3	4	1	1	1	1	1	4	1	1	1	1	3	1	1	1	1	1	1	1	5	1	3	5	2	3	2	1	1	4	1	3

Fig. 1. (*continued*).

(NCT03668431) evaluated the combination of dabrafenib + trametinib with spartalizumab, a programmed cell death 1 (PD-1) inhibitor. Preliminary data demonstrated an ORR of 35% in patients with $BRAF^{V600E}$-mutant CRC (n = 20); 42% in patients with MSS disease who had not previously been treated with BRAF inhibitors or immune checkpoint inhibitors (n = 12); and 25% in patients with MSI disease (n = 4) [80,81]. A phase 1 study (NCT04294160) is evaluating dabrafenib in combination with PD-1 inhibitors (spartalizumab, tislelizumab) and a MEK inhibitor (trametinib) as well as other novel treatment strategies, including a BRAF/CRAF inhibitor (LXH254), ERK1/2 inhibitor (LTT462), and SHP2 inhibitor (TNO155) [67,82].

In addition to developing new treatments and improving existing ones, there are several other pressing avenues for future research. Resistance to targeted therapy develops systematically, and potential mechanisms of acquired resistance is a critical area of interest for future research [83]. An analysis of ctDNA profiles from patients in the BEACON study found MAPK pathway reactivation to be common in patients with $BRAF^{V600E}$-mutant mCRC treated with encorafenib + cetuximab ± binimetinib; the most common acquired resistance alterations were *KRAS/NRAS* mutations and *MET* amplification [84].

New predictive biomarkers are needed to identify subpopulations that may benefit from specific treatments [85]. Barras et al. proposed subdividing *BRAF*-mutant mCRC into $BRAF^{V600E}$ mutation (BM) subtypes based on gene expression: BM1 is characterised by highly active KRAS/AKT/mTOR/4EBP signalling and epithelial–mesenchymal transition, and BM2 by cell cycle deregulation [86]. Furthermore, upon treatment with a combination of BRAF, EGFR, and MEK inhibitors, patients of the BM1 subtype experienced greater clinical benefits than those of the BM2 subtype [87]. Using whole-exome sequencing, Elez, et al found an *RNF43* mutation in patients with MSS $BRAF^{V600E}$-mutant mCRC to be predictive of improved ORR and longer PFS and OS in response to treatment with BRAF and EGFR inhibitors, with or without MEK inhibitors [85]. In another analysis, Elez, et al found the *BRAF* mutant allele fraction (MAF; the proportion of mutant alleles in cell-free DNA) to be an independent prognostic biomarker and surrogate for tumour load; higher *BRAF* MAF was correlated with a shorter OS and associated with a more aggressive disease [88]. Finally, in *BRAF*-mutant mCRC, MSS tumours are known to have a poor prognosis; however, in MSI tumours, *BRAF* mutations do not appear to adversely affect outcomes [36,89].

Table 4
Overview of key ongoing studies in *BRAF*^{V600E}-mutant mCRC.

Study	Phase	Treatment arm(s)	Estimated sample size and population	Efficacy outcomes
BREAKWATER (NCT04607421) [59,60,90]	3	• Encorafenib + cetuximab • Encorafenib + cetuximab + mFOLFOX6 • mFOLFOX6/FOLFIRI/CAPOX • mFOLFOX6/FOLFIRI/CAPOX + bevacizumab	N = 870; untreated	Safety lead-in: ORR: First-line encorafenib + cetuximab + mFOLFOX6: 68.4% First-line encorafenib + cetuximab + FOLFIRI: 66.7% Second-line encorafenib + cetuximab + mFOLFOX6: 50.0% Second-line encorafenib + cetuximab + FOLFIRI: 61.1% Median PFS: First-line encorafenib + cetuximab + mFOLFOX6: 9.9 months First-line encorafenib + cetuximab + FOLFIRI: not estimable Second-line encorafenib + cetuximab + mFOLFOX6: 9.7 months Second-line encorafenib + cetuximab + FOLFIRI: not estimable
SEAMARK (NCT05217446) [75]	2	• Encorafenib + cetuximab + pembrolizumab • Pembrolizumab	N = 104; untreated; MSI-high/dMMR	Not applicable (N/A)
NCT04017650 [76]	1/2	• Encorafenib + cetuximab + nivolumab	N = 26; previously treated; MSS	ORR: 45% Median PFS: 7.3 months Median OS: 11.4 months
SWOG 2107 (NCT05308446) [78]	2	• Encorafenib + cetuximab • Encorafenib + cetuximab + nivolumab	N = 84; previously treated; MSS/pMMR	N/A
NCT03668431 [80,81]	2	• Dabrafenib + trametinib + spartalizumab	N = 21; untreated and previously treated; MSI and MSS	ORR: 35%ORR (MSS; untreated) : 42%ORR (MSI) : 25%
NCT04294160 [82]	1	• Dabrafenib + LTT462 • Dabrafenib + LTT462 + trametinib • Dabrafenib + LTT462 + LXH254 • Dabrafenib + LTT462 + TNO155 • Dabrafenib + LTT462 + spartalizumab • Dabrafenib + trametinib + TNO155 • Dabrafenib + LTT462 + tislelizumab	N = 350; previously treated	N/A

Abbreviations: dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MSI, microsatellite instable; MSS, microsatellite stable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pMMR, proficient mismatch repair.

Conclusions

There have been significant and meaningful advances in the treatment of *BRAF*^{V600E}-mutant mCRC in the last few years. *BRAF* testing is now recommended in the current ESMO clinical guidelines for all patients diagnosed with mCRC [18]. The approval of targeted therapies in the second line has improved the management of patients with *BRAF*^{V600E}-mutant mCRC. We keenly await data from ongoing trials, which will be pivotal in informing the rational use of targeted and combined therapies in the future.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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