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Expert consensus on the optimal management of *BRAF*^{V600E}-mutant metastatic colorectal cancer in the Asia-Pacific region

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Abstract

The burden of colorectal cancer (CRC) is high in the Asia-Pacific region, and several countries in this region have among the highest and/or fastest growing rates of CRC in the world. A significant proportion of patients will present with or develop metastatic CRC (mCRC), and *BRAF*^{V600E}-mutant mCRC represents a particularly aggressive phenotype that is less responsive to standard chemotherapies. In light of recent therapeutic advances, an Asia-Pacific expert consensus panel was convened to develop evidence-based recommendations for the diagnosis, treatment, and management of patients with *BRAF*^{V600E}-mutant mCRC. The expert panel comprised nine medical oncologists from Australia, Hong Kong, Singapore, and Taiwan (the authors), who met to review current literature and develop eight consensus statements that describe the optimal management of *BRAF*^{V600E}-mutant mCRC in the Asia-Pacific region. As agreed by the expert panel, the consensus statements recommend molecular testing at diagnosis to guide individualized treatment decisions, propose optimal treatment pathways according to microsatellite stability status, advocate for more frequent monitoring of *BRAF*^{V600E}-mutant mCRC, and discuss local treatment strategies for oligometastatic disease. Together, these expert consensus statements are intended to optimize treatment and improve outcomes for patients with *BRAF*^{V600E}-mutant mCRC in the Asia-Pacific region.

KEYWORDS

Asia-Pacific, *BRAF*^{V600E} mutation, immunotherapy, metastatic colorectal cancer, targeted therapy

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1 | INTRODUCTION

Colorectal cancer (CRC) is the third-most diagnosed cancer and second-leading cause of cancer death worldwide, accounting for more than 1.9 million new cases and 930,000 deaths in 2020.[1,2] The burden of CRC is particularly high in the Asia-Pacific region; Australia, New Zealand, Japan, and Singapore have among the highest rates of CRC in the world, whereas countries in East, South, and South-East Asia have among the fastest growing rates of CRC globally.[2,3] A significant proportion of patients diagnosed with CRC will present with or subsequently develop metastatic CRC (mCRC), which remains largely incurable.[4,5]

mCRC is a highly heterogeneous disease, with several subtypes characterized according to key genetic alterations.[6] Importantly, mCRC subtypes have become increasingly targetable with molecularly directed therapies, which provide new opportunities to individualize treatment pathways and improve patient outcomes.[6] Consequently, treatment options for mCRC have expanded beyond chemotherapy in recent decades and now include targeted molecular therapies and immune checkpoint inhibitors (ICIs) for certain subgroups.

mCRC harboring mutations in the *BRAF* (B-Raf proto-oncogene serine/threonine-protein kinase) gene, most frequently $BRAF^{V600E}$, occur in approximately 10% of patients, representing a particularly aggressive phenotype and an area of unmet research need.[7–13] In light of significant therapeutic advances for patients with $BRAF^{V600E}$-mutant mCRC, an Asia-Pacific expert consensus panel was assembled to review current evidence and provide recommendations for the diagnosis, treatment, and monitoring of $BRAF^{V600E}$-mutant mCRC in the region.

2 | EXPERT CONSENSUS METHODS AND RESULTS

Nine medical oncologists from Australia, Hong Kong, Singapore, and Taiwan (the authors) formed an expert consensus panel based on their expertise in $BRAF^{V600E}$-mutant mCRC management in the Asia-Pacific region (e.g., participation in $BRAF^{V600E}$-mutant mCRC research and clinical trials, relevant publication history, and clinical experience of managing $BRAF^{V600E}$-mutant mCRC in high-volume or specialized treatment centers). Two meeting co-chairs (OP and JD) reviewed relevant literature and drafted preliminary topics and clinical questions to be discussed at the consensus meetings.

In May 2023, two virtual expert consensus meetings were held to discuss the optimal management of $BRAF^{V600E}$-mutant mCRC in the Asia-Pacific region. Two meetings ensured that all expert panel members could participate across time zones and attend at least one meeting. Both meetings were led by the two co-chairs and followed the same agenda to give all experts the opportunity to contribute to all topics.

Based on the discussions, the meeting co-chairs developed draft consensus statements that were shared with all experts for review and refinement. Once approved, the consensus statements were circulated in an online poll, and all experts voted independently and anonymously on their level of agreement with each statement. Level of agreement was rated on a scale from 1 (strongly disagree) to 5 (strongly agree), and free text fields allowed experts to provide additional feedback on each statement. Consensus was reached when ≥7 of 9 experts voted with an agreement level of 4 or 5, and the level of consensus among experts was further graded using criteria in Table 1.

TABLE 1 Definitions for the level of agreement with each consensus statement, and the level of consensus reached among the Asia-Pacific expert panel.

Level of agreement with each statement[a]	Definition
1	Strongly disagree
2	Disagree
3	Neutral
4	Agree
5	Strong agree
Level of consensus for each statement	**Definition**
A	9 of 9 experts voted with agreement level 4 or 5
B	8 of 9 experts voted with agreement level 4 or 5
C	7 of 9 experts voted with agreement level 4 or 5

[a]Free text fields allowed experts to provide additional anonymous feedback on each statement.

2.1 | Consensus statements

In August 2023, the expert panel voted on eight consensus statements that described the optimal management of $BRAF^{V600E}$-mutant mCRC in the Asia-Pacific region. The consensus statements agreed by the experts are provided in Table 2 and contextualized in the following sections. A suggested treatment algorithm for $BRAF^{V600E}$-mutant mCRC, based on these consensus statements, is presented in Figure 1.

3 | CRC IN THE ASIA-PACIFIC REGION

Recent estimates of the global age-standardized incidence rate of CRC have ranged between 19.6 and 26.7 cases per 100,000, with wide variations across world regions and countries.[2,3] In the Asia-Pacific region, rates of new CRC diagnoses range from 5.5–15.2 cases per 100,000 in South-Central Asia up to 33.2–48.3 cases per 100,000 in Australia and New Zealand.[2,3]

Higher rates of CRC are often reported in countries with greater socioeconomic development.[2,3] Although this may be partly due to greater life expectancy, it is also likely to reflect differences in modifiable risk factors (e.g., obesity, physical inactivity, diet, smoking, and

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TABLE 2 Expert consensus statements for the optimal management of *BRAF*^{V600E}-mutant mCRC in the Asia-Pacific region.

Consensus statement	Level of consensus
1. At diagnosis, all patients with mCRC should have molecular testing to assess for mutations in *KRAS/NRAS* (Exons 2–4) and *BRAF*^{V600E}, as well as testing for MMR status, in order to plan the most appropriate first and later lines of therapy	A
2. The preferred method to confirm *BRAF*^{V600E} mutational status in mCRC is with NGS	B
3. Patients with *BRAF*^{V600E}-mutant mCRC and good performance status should be considered for enrolment in available clinical trials testing novel or combination therapies incorporating BRAF/EGFR inhibition	A
4. For patients with MSS *BRAF*^{V600E}-mutant mCRC, the preferred first-line treatment is doublet chemotherapy plus bevacizumab, with consideration for triplet chemotherapy plus bevacizumab in some circumstances (e.g., young patients with good performance status, patients with heavy burden of disease, potentially resectable disease depending on response)	B
5. For patients with MSS *BRAF*^{V600E}-mutant mCRC, the preferred second-line therapy is encorafenib and cetuximab	A
6. For patients with MSI-high or dMMR *BRAF*^{V600E}-mutant mCRC, the preferred first-line therapy is pembrolizumab	A
7. Patients with *BRAF*^{V600E}-mutant mCRC should be considered for more frequent restaging imaging (every 6–8 weeks) while receiving first-line therapy to avoid delays in detecting disease progression and changing to another therapy	A
8. Management of oligometastatic disease with surgery or local ablative therapies in *BRAF*^{V600E}-mutant mCRC should only be considered in carefully selected patients. This may include patients who have demonstrated durable disease stability during systemic treatment, have had adequate staging as appropriate to rule out other occult sites of disease, and have been discussed in a multidisciplinary tumor board	C

Abbreviations: BRAF, B-Raf proto-oncogene serine/threonine-protein kinase; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; NGS, next-generation sequencing; NRAS, neuroblastoma RAS viral oncogene homolog.

alcohol consumption).[2,3] Temporal analyses show that the incidence and mortality of CRC in higher income countries have plateaued or decreased in recent years, due in part to increased screening and early detection of precancerous lesions in older adults (typically aged >50 years).[3,4,14] However, studies have also revealed increasing CRC incidence in lower- and middle-income countries, particularly in Asia.[2,3] This may be associated with rapid economic growth and increased adoption of westernized lifestyles in these transitioning countries.

Consistent with other parts of the world, the incidence of CRC among younger individuals (typically aged <50 years) is rising in the Asia-Pacific region.[2–4,14–16] Although the reasons for this trend are not clearly defined, the birth cohort effect (i.e., lifelong exposure to modifiable risk factors) is hypothesized to play a key role.

4 | PATHOLOGICAL AND CLINICAL FEATURES OF *BRAF*^{V600E}-MUTANT mCRC

Approximately 20%–30% of patients diagnosed with CRC present with metastases (most often in the liver, lungs, peritoneum, and lymph nodes), and up to 50% of patients who initially have early-stage CRC will eventually develop metastatic disease.[6,17] Despite increased understanding of its molecular heterogeneity and recent therapeutic advances, mCRC continues to be associated with poor prognosis, with estimated 5-year overall survival (OS) rates of 10%–30%.[4,18,19]

BRAF mutations are strong negative prognostic markers in patients with mCRC.[7–13,20] *BRAF* is a proto-oncogene that encodes the serine/threonine kinase BRAF, which is an essential component of the mitogen-activated protein kinase (MAPK) pathway.[13,21,22] The MAPK pathway is an important regulator of cell proliferation, differentiation, migration, and survival; therefore, dysregulated MAPK signaling has been implicated in the pathogenesis of multiple cancer types, including CRC.

In CRC, the most frequently observed mutation in *BRAF* (~80%–90%) is due to a point mutation within exon 15 that substitutes valine for glutamic acid at codon 600 (V600E).[12,23–26] Such *V600* mutations (Class I) allow BRAF to function as a RAS-independent monomer, in contrast to physiologic RAS-dependent dimer signaling, leading to constitutive activation of the MAPK pathway and increased cancer cell proliferation and survival.[12,23] Thus, the *BRAF*^{V600E} mutation is almost always mutually exclusive with upstream *RAS* mutations.[27,28]

The less common, "atypical" non-V600 *BRAF* mutations occur in approximately 2% of patients with mCRC and increase MAPK signaling either through acting as RAS-independent BRAF mutant dimers (Class II), or RAS-dependent heterodimers (Class III). Class II and III mutations increase MAPK signaling to a lesser magnitude than Class I and are associated with better prognosis.[24–26] As such, the recommendations from this consensus guideline specifically refer to patients with *BRAF*^{V600E}-mutant mCRC.

BRAF^{V600E}-mutant mCRC is strongly associated with microsatellite instability (MSI), and approximately 30% of these tumors are MSI-high.[10,21,28,29] This is consistent with the finding that *BRAF*^{V600E}-mutant mCRC is associated with the CpG island methylation phenotype, characterized by hypermethylation and silencing of the *MLH1* promoter gene, which causes sporadic MSI.[30]

BRAF^{V600E}-mutant mCRC may be further classified according to gene expression profiles. Based on the CRC consensus molecular subtypes (CMS1–4), the majority (>70%) can be classified as CMS1 ("MSI, immune"), 17% as CMS4 ("mesenchymal"), whereas less than 10% are classified as CMS2 ("Canonical") or CMS3 ("Metabolic").[31,32]

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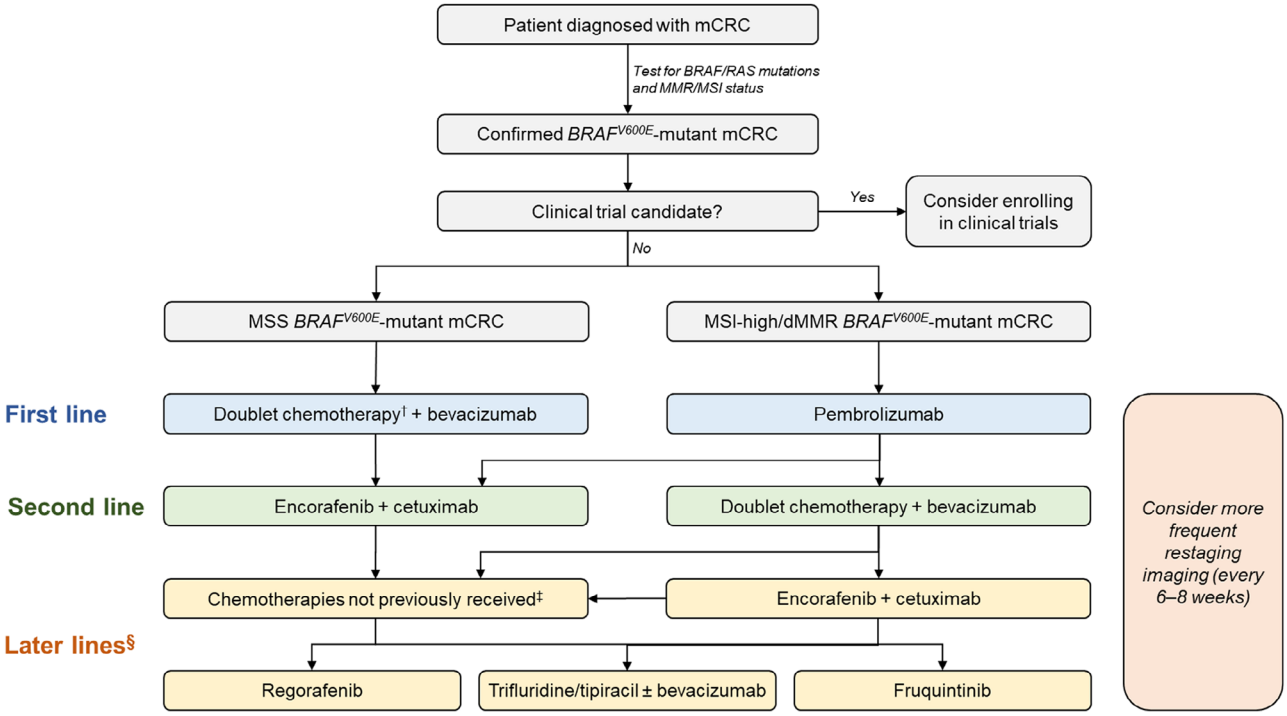

FIGURE 1 Suggested treatment algorithm for patients with *BRAF*^{V600E}-mutant mCRC, based on Asia-Pacific expert consensus statements. †Patients should receive doublet chemotherapy with fluoropyrimidine plus either oxaliplatin or irinotecan; consider triplet chemotherapy in some circumstances (e.g., young patients with good performance status, patients with heavy burden of disease, potentially resectable disease depending on response). ‡Patients should receive fluoropyrimidine plus either oxaliplatin or irinotecan, if not previously received. §Later lines of therapy are not well studied in patients with *BRAF*^{V600E}-mutant mCRC. dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable.

BRAF-mutant (BM) transcriptional subtypes have also been proposed to specifically subclassify *BRAF*^{V600E}-mutant CRC tumors. Using this tool, approximately 30% can be categorized as BM1 (enriched for upregulated phosphoinositide 3-kinase/Akt pathway activity) and 70% as BM2 (enriched for upregulated cell-cycle activity and MSI).[29,32]

In Australia, *BRAF*^{V600E} mutations have been reported in approximately 8%–12% of mCRC cases, similar to other countries with predominantly Caucasian populations.[8,10,12,29] In Asia, the prevalence of *BRAF*^{V600E} mutations in CRC is comparatively lower.[33] It has been estimated at 5.6% overall, but with wide variation across the region, from 1.1% in Taiwan to 14.0% in Indonesia.[34,35]

Clinical factors associated with *BRAF*^{V600E}-mutant mCRC include older age at diagnosis, female sex, and right-sided tumors with mucinous histology.[8,10,11,13,28] *BRAF*^{V600E}-mutant mCRC also exhibits a distinct pattern of metastatic spread, characterized by more frequent peritoneal and nodal metastases, a trend for more frequent brain metastases, and less frequent liver-limited and lung metastases versus *BRAF* wild-type tumors.[10,11,36] *BRAF*^{V600E}-mutant mCRC represents an aggressive phenotype that is less responsive to standard chemotherapy regimens[8]; median progression-free survival (PFS) is approximately 6 months with first-line chemotherapy, which falls to <3 months in patients who receive second- and third-line chemotherapy.[37,38] These data highlight the importance of identifying patients with *BRAF*^{V600E}-mutant mCRC and adopting individualized treatment strategies to improve outcomes for this population.

5 | MOLECULAR TESTING IN mCRC

Given that genomic alterations in mCRC can inform treatment decisions and survival outcomes, international clinical practice guidelines recommend that patients with mCRC should be tested for *BRAF* and *RAS* mutations and mismatch repair (MMR)/MSI status at diagnosis.[17,39–42] More specifically, *BRAF*^{V600E} mutation testing is recommended to assess prognosis and suitability for encorafenib/cetuximab therapy, tests for *KRAS* and *NRAS* (Exons 2–4) mutations are recommended to determine benefit from epidermal growth factor receptor (EGFR) inhibitors, and assessment of MMR/MSI status is recommended to identify patients at risk of Lynch syndrome and those indicated for immunotherapy (consensus statement 1; Table 2).

We acknowledge that the availability and reimbursement of next-generation sequencing (NGS) tests for mCRC varies across the Asia-Pacific,[41] and that immunohistochemical (IHC) assays are rapid, inexpensive, and commonly used methods that demonstrate good concordance with sequencing-based techniques.[43] However, we recommend that *BRAF*^{V600E} mutational testing should be carried out using NGS wherever feasible, for consistency with clinical trials that used NGS-based testing to identify and enroll patients with *BRAF*^{V600E}-mutant mCRC (consensus statement 2; Table 2). Nevertheless, we agree that a two-step testing approach (i.e., IHC followed by confirmatory NGS) could be considered acceptable in clinical settings where resources preclude a single-step, NGS-only approach.

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6 | OPTIMAL MANAGEMENT OF MICROSATELLITE STABLE *BRAF*^{V600E}-MUTANT mCRC

6.1 | First-line therapy

After diagnosis and molecular testing, patients with confirmed *BRAF*^{V600E}-mutant mCRC should be encouraged to participate in clinical trials evaluating novel or combination therapies (consensus statement 3; Table 2). When clinical trial participation is not feasible, first-line chemotherapy plus bevacizumab remains the standard of care for patients with microsatellite stable (MSS) *BRAF*^{V600E}-mutant mCRC (consensus statement 4; Table 2; Figure 1).

Our consensus statement is in line with current international guidelines, which recommend first-line doublet or triplet chemotherapy, with or without vascular endothelial growth factor (VEGF) inhibition with bevacizumab, in patients with unresectable MSS *BRAF*^{V600E}-mutant mCRC.[17,41,42,44] Doublet chemotherapy is preferred in most cases; FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and FOLFIRI (folinic acid, fluorouracil, and irinotecan) have been shown to be equally effective,[45–48] whereas CAPOX (capecitabine plus oxaliplatin) is noninferior to FOLFOX and can also be considered.[44,49]

Adding biologics to first-line chemotherapy, particularly EGFR inhibitors (e.g., cetuximab, panitumumab) or VEGF inhibitors (e.g., bevacizumab), has been shown to improve outcomes in the overall mCRC population.[50,51] However, anti-EGFR therapy with or without chemotherapy (and without a BRAF inhibitor) has demonstrated limited benefit in *BRAF*-mutant subgroups[52–54] and is not recommended for these patients in the first-line setting.[17] In comparison, the survival advantages of adding anti-VEGF therapy to chemotherapy are preserved in patients with *BRAF*-mutant mCRC[55]; therefore, first-line chemotherapy plus bevacizumab is recommended unless otherwise contraindicated.

The decision to initiate first-line doublet or triplet chemotherapy was evaluated in the Phase 3 TRIBE study, which compared FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan) plus bevacizumab with FOLFIRI plus bevacizumab in 508 patients with untreated mCRC.[56] Triplet chemotherapy plus bevacizumab was associated with significant improvements in median PFS (12.1 vs. 9.7 months; $p = 0.003$) and nonsignificant improvements in median OS (31.0 vs. 25.8 months; $p = 0.054$) versus doublet chemotherapy plus bevacizumab.[56] In a post hoc analysis of the *BRAF*-mutant subgroup ($n = 28$), PFS and OS were numerically longer with triplet versus doublet chemotherapy plus bevacizumab (median PFS: 7.5 vs. 5.5 months; median OS: 19.0 vs. 10.7 months), but these results were not statistically significant.[57] A subsequent meta-analysis of five randomized trials ($n = 1697$, including 115 patients with *BRAF*-mutant mCRC) concluded that first-line FOLFOXIRI plus bevacizumab does not confer any significant survival advantage over doublet chemotherapy plus bevacizumab for *BRAF*-mutant mCRC (median OS: 13.6 vs. 14.5 months, respectively).[58] Based on these data, we recommend that doublet chemotherapy should form the backbone of first-line treatment for patients with MSS *BRAF*^{V600E}-mutant mCRC, whereas intensive triplet chemotherapy may be considered for selected subgroups (e.g., young patients with good performance status, patients with heavy disease burden who are expected to tolerate a triplet approach, and those with potential for resection depending on response).

6.2 | Second-line therapy

Despite its demonstrable efficacy in *BRAF*^{V600E}-mutant melanoma,[59] targeted therapy with single-agent BRAF inhibitors (e.g., vemurafenib, dabrafenib) has limited response in patients with *BRAF*^{V600E}-mutant mCRC.[60,61] Moreover, only modest improvements in efficacy are observed when BRAF inhibitors are combined with MEK inhibitors (e.g., trametinib, cobimetinib, binimetinib).[61–63] Under physiological conditions, activation of extracellular signal-regulated kinases (ERK) in the MAPK pathway suppresses EGFR activation via negative feedback through phosphatase Cdc25C, and preclinical studies have shown that BRAF inhibition paradoxically and rapidly reactivates EGFR and MAPK signaling.[61,64,65] These data provided a strong rationale to study combined EGFR and BRAF blockade as a strategy to overcome BRAF inhibitor resistance in *BRAF*^{V600E}-mutant mCRC; indeed, preclinical studies have demonstrated reduced MAPK signaling and increased efficacy when EGFR and BRAF inhibitors are combined.[61,64–67]

The pivotal BEACON CRC trial evaluated dual EGFR and BRAF inhibition with encorafenib plus cetuximab, with or without MEK inhibition using binimetinib, in patients with *BRAF*^{V600E}-mutant mCRC.[68,69] In this global Phase 3 study, 665 patients with disease progression after 1–2 prior lines of therapy were randomized to receive doublet therapy (encorafenib/cetuximab), triplet therapy (encorafenib/cetuximab plus binimetinib), or control treatment (irinotecan-based chemotherapy plus cetuximab).[68,69] Compared with control, the doublet and triplet therapies were each associated with significant improvements in median OS (9.3 and 9.3 months vs. 5.9 months, respectively), median PFS (4.3 and 4.5 months vs. 1.5 months), and objective response rate (ORR; 19.5% and 26.8% vs. 1.8%; Table 3).[69] Both the doublet and triplet therapies demonstrated an acceptable safety profile; the incidence of grade ≥3 adverse events (AEs) was 57.4%, 65.8%, and 64.2% in the doublet, triplet, and control groups, respectively, and treatment discontinuation due to an AE was low, occurring in 9%, 9%, and 11% of patients across arms.[69]

Based on the finding that doublet therapy demonstrated superior efficacy versus control and improved toxicity versus triplet therapy,[68,69] encorafenib/cetuximab was approved in the United States and European Union in 2020 for the treatment of adults with *BRAF*^{V600E}-mutant mCRC after ≥1 prior line of therapy.[70,71] Encorafenib/Cetuximab is now approved for this indication in many countries across the Asia-Pacific region, and several others are expected to gain approval and access to this treatment option in the future. In Japan, the triplet combination of encorafenib/cetuximab plus binimetinib was additionally approved based on signals suggestive of improved efficacy in some BEACON CRC subgroups (e.g., patients

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TABLE 3 Key studies of targeted therapy strategies for patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer.

Study (CT.gov identifier)	Study design	*BRAF*^{V600E}-mutant mCRC population	Intervention	Comparator	Key efficacy outcomes
BEACON CRC (NCT02928224)[69]	Randomized, open-label, Phase 3 study	Patients with progression after 1–2 prior treatment lines	Doublet: encorafenib + cetuximab ($n = 220$) Triplet: encorafenib + binimetinib + cetuximab ($n = 224$)	Cetuximab + irinotecan or cetuximab + FOLFIRI ($n = 221$)	Doublet vs. control: ORR = 19.5% vs. 1.8% ($p < 0.0001$) Median PFS: 4.3 vs. 1.5 months Median OS: 9.3 vs. 5.9 months Triplet vs. control: ORR = 26.8% vs. 1.8% ($p < 0.0001$) Median PFS: 4.5 vs. 1.5 months Median OS: 9.3 vs. 5.9 months
ANCHOR CRC (NCT03693170)[152]	Single-arm, Phase 2 study	Previously untreated patients	Encorafenib + binimetinib + cetuximab ($n = 95$)	None	ORR = 47.8% Median PFS = 5.8 months Median OS = 18.3 months
EVICT[66]	Single-arm, Phase 1b/2 study	Previously treated patients (≤2 prior lines)	Vemurafenib + erlotinib ($n = 31$)	None	ORR = 32% Median PFS = 3.9 months Median OS = 6.3 months
IMPROVEMENT (NCT03727763)[153]	Single-arm, Phase 2 study	Treatment-naïve or previously treated patients (≤2 prior lines)	Cetuximab + vemurafenib + FOLFIRI ($n = 21$)	None	ORR = 81% Median PFS = 9.7 months Median OS = 15.4 months
MODUL (NCT02291289)[154]	Randomized, open-label, Phase 2 study	Previously untreated patients without disease progression following standard induction therapy (5-FU/LV + oxaliplatin + bevacizumab)	Vemurafenib + cetuximab + 5-FU/LV ($n = 40$)	Fluoropyrimidine + bevacizumab ($n = 20$)	ORR = 50.0% vs. 25.0% ($p = 0.064$) Median PFS = 10.0 vs. 11.6 months ($p = 0.87$) Median OS = 24.0 vs. 21.3 months ($p = 0.29$)
NCT03668431[155]	Single-arm, Phase 2 study	Treatment-naïve or previously treated patients	Spartalizumab + dabrafenib + trametinib ($n = 37$)	None	ORR = 24.3% Median PFS = 4.3 months Median OS = 13.6 months
NCT04017650[156]	Single-arm, Phase 1/2 study	Patients with treatment-refractory MSS mCRC	Encorafenib + cetuximab + nivolumab ($n = 26$)	None	ORR = 45% Median PFS = 7.3 months Median OS = 11.4 months
SWOG S1406 (NCT02164916)[157]	Randomized, Phase 2 study	Previously treated patients (1–2 prior lines)	Cetuximab + irinotecan + vemurafenib ($n = 50$)	Cetuximab + irinotecan ($n = 50$)	ORR = 17% vs. 4% Median PFS = 4.2 vs. 2.0 months ($p = 0.001$) Median OS = 9.6 vs. 5.9 months ($p = 0.23$)

Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin; CT.gov, ClinicalTrials.gov; FOLFIRI, folinic acid, fluorouracil, and irinotecan; mCRC, metastatic colorectal cancer; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SWOG, Southwest Oncology Group.

TABLE 4 Clinical management recommendations for adverse events associated with encorafenib/cetuximab therapy reported in the BEACON colorectal cancer (CRC) study.[68,69,74–76]

Safety findings from BEACON CRC	Clinical management recommendations
• Most common AEs (any grade) in the encorafenib/cetuximab arm: diarrhea (38%), nausea (38%), fatigue (33%), acneiform dermatitis (30%) ○ Most AEs occurred early (within the first 1–2 months) and resolved within 1–2 weeks without treatment discontinuation ○ Dermatological AEs and arthralgias/myalgias may take longer to resolve (3–6 weeks)	• Monitor patients closely during the first 2 months of treatment • Ensure patients have anti-diarrhea and anti-nausea medications • Acneiform dermatitis is often manageable with moisturizers, hydrocortisone, tetracyclines
• Incidence of AEs was greater in some subgroups ○ Women: nausea/vomiting, diarrhea, abdominal pain, dermatological AEs, arthralgia/myalgia ○ Elderly (≥70 years): nausea/vomiting, abdominal pain, fatigue/asthenia	• Recommend close monitoring for AEs in these patients
• Grade ≥3 AEs reported in 57% of patients in the encorafenib/cetuximab arm ○ Most common grade ≥3 AEs: fatigue (4%), asthenia (4%), abdominal pain (3%), diarrhea (3%)	• For grade ≥3 AEs, a short-dose interruption is recommended • Once improved, consider reintroducing treatment at a lower dose, rather than permanent discontinuation
• Specific encorafenib-related AEs: arthralgia/myalgia (56%), fever (19%), prolonged QT interval (9%), melanoma (2%), keratoacanthoma (1%)	• Arthralgia/Myalgia: advise rest, stretching, as-needed paracetamol, and low-dose steroids in severe cases • Fever: rule out infection, then advise supportive care, including antipyretics, fluids, and rest • Prolonged QT interval: recommend ECG at baseline, after 1 month, then every 3 months thereafter; review concomitant medications that may also prolong QT intervals • Cutaneous malignancies: recommend at least 6-monthly dermatological assessments during treatment • Avoid co-administration of encorafenib with cytochrome P450 3A4 inhibitors and inducers

Abbreviations: AE, adverse event; ECG, electrocardiogram.

with Eastern Cooperative Oncology Group performance status of 1, ≥3 organs involved, unresected or partially resected primary tumor).[41,69,72,73]

Our consensus statement is consistent with current clinical guidelines and recognizes that targeted therapy with encorafenib/cetuximab is the standard of care for patients with previously treated *BRAF*^{V600E}-mutant mCRC (consensus statement 5; Table 2).[17,41,44] Although BEACON CRC evaluated encorafenib/cetuximab in the second- and third-line settings,[68,69] we recommend initiating treatment as soon as possible after first-line progression. BEACON CRC demonstrated that responses to subsequent-line chemotherapy are relatively poor for those with *BRAF*^{V600E}-mutant mCRC; therefore, we believe that these patients should receive and benefit from encorafenib/cetuximab at their earliest opportunity.

Given that encorafenib/cetuximab displays a distinct safety profile, with some AEs requiring more than standard supportive care,[74–77] management recommendations for common treatment-related AEs are provided in Table 4. Nevertheless, a recent in-depth safety analysis of BEACON CRC confirmed that encorafenib/cetuximab was generally well tolerated; most AEs occurred within the first 1–2 months of treatment and resolved in 1–2 weeks without treatment discontinuation, and most grade ≥3 AEs were managed with a short dose interruption.[76]

The incidence of cetuximab-induced hypersensitivity infusion reactions has been estimated at 8.4% across clinical trials (including severe reactions in 2.2% of patients)[78]; however, real-world studies have revealed increased rates of infusion reactions in some regions.[79–82] Cetuximab-induced anaphylaxis is more common among patients with immunoglobulin E (IgE) antibodies raised against galactose-α-1,3-galactose (α-gal), an oligosaccharide present on the antigen-binding fragment of the cetuximab heavy chain.[80,83] Tick bites are a key cause of α-gal sensitivity and cetuximab-induced anaphylaxis[81,82,84]; therefore, patients in tick-prevalent regions should be tested for α-gal-specific IgE antibodies before treatment with cetuximab.[85] Case report data suggest that patients with α-gal IgE positivity could be considered for treatment with an alternative EGFR inhibitor, namely, panitumumab, which does not contain the α-gal epitope.[86–90]

Currently, BEACON CRC represents the largest randomized controlled trial, and only Phase 3 study, of molecularly targeted therapy in patients with *BRAF*^{V600E}-mutant mCRC. However, several smaller, earlier phase studies have assessed the efficacy of other targeted therapy strategies in this population, as summarized in Table 3.

6.3 | Later lines of therapy

Effective third- and later-line therapies are limited for patients with MSS *BRAF*^{V600E}-mutant mCRC. In the absence of specific guidance for the *BRAF*^{V600E}-mutant population, clinical guidelines suggest

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that patients who are well enough should be exposed to all active chemotherapies that they have not previously received, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens.[17,41] Thereafter, regorafenib (multi-kinase inhibitor), trifluridine/tipiracil (thymidine analogue/thymidine phosphorylase inhibitor; with or without bevacizumab), or fruquintinib (VEGF receptor 1–3 inhibitor) can be considered for patients with refractory mCRC who have previously received all available standard chemotherapy and targeted therapy regimens (Figure 1).[17,41,42]

These recommendations are based on clinical trials that demonstrated survival benefits with regorafenib[91–93] and trifluridine/tipiracil[94,95] versus best supportive care for refractory mCRC. Trifluridine/tipiracil can be used with or without bevacizumab based on data from the RECOURSE and SUNLIGHT trials,[94,96] whereas fruquintinib may also be considered, even after failure of trifluridine/tipiracil or regorafenib, based on OS benefits reported in the FRESCO-1 and FRESCO-2 studies.[97,98] However, we reiterate that the efficacy and safety of these therapies in *BRAF*^{V600E}-mutant mCRC specifically are not well described.

Resistance to targeted therapies in *BRAF*^{V600E}-mutant mCRC can occur when acquired genetic alterations restore MAPK signaling.[99–102] However, it has also been observed that *RAS* mutant clones decay after emerging in response to EGFR inhibition in *RAS* and *BRAF* wild-type mCRC, suggesting that "rechallenge" strategies may show promise in patients who were previously sensitive to targeted therapies.[103] To test this hypothesis, the ongoing Phase 2 TRIDENTE study will evaluate the safety and efficacy of rechallenge therapy with encorafenib, cetuximab, and binimetinib in patients with refractory *BRAF*^{V600E}-mutant mCRC.[104]

7 | OPTIMAL MANAGEMENT OF MSI-HIGH *BRAF*^{V600E}-MUTANT mCRC

7.1 | First-line therapy

ICI therapies (e.g., pembrolizumab, nivolumab, and ipilimumab) have become an efficacious treatment option for patients with MSI-high mCRC.[105–108] In line with our consensus statement, current clinical guidelines recommend pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, for the first-line treatment of patients with MSI-high or deficient MMR (dMMR) mCRC (consensus statement 6; Table 2).[17,41,44] Based on promising interim PFS data from the Phase 3 CheckMate 8HW trial, nivolumab (PD-1 inhibitor) plus ipilimumab (cytotoxic T-lymphocyte-associated protein 4 inhibitor) may become an additional first-line treatment option for these patients in future clinical practice.[109,110]

Nevertheless, our current recommendation is largely informed by the phase 3 KEYNOTE-177 trial, which compared pembrolizumab with standard chemotherapy (FOLFOX or FOLFIRI, with or without cetuximab or bevacizumab) in 307 patients with untreated MSI-high/dMMR mCRC.[106,111] First-line pembrolizumab was associated with significantly longer median PFS versus chemotherapy (16.5 vs. 8.2 months; $p = 0.0002$) and fewer treatment-related grade ≥3 AEs (22% vs. 66%).[106,111] Although the difference in OS between the pembrolizumab and chemotherapy arms was not statistically significant at the prespecified final analysis (median OS not reached vs. 36.7 months, respectively), the true magnitude of pembrolizumab benefit may be less apparent because 60% of patients in the chemotherapy arm subsequently received ICI therapy.[111] Indeed, recent 5-year follow-up data from KEYNOTE-177 revealed that median OS associated with first-line pembrolizumab was more than double than that achieved with chemotherapy (77.5 vs. 36.7 months; hazard ratio [HR]: 0.73; 95% CI: 0.53–0.99).[112]

A trend for improved OS with pembrolizumab versus chemotherapy was similarly observed in the subgroup of patients with *BRAF*^{V600E}-mutant tumors ($n = 81$; median OS: not reached vs. 45.2 months).[111] This is consistent with real-world reports that survival outcomes with ICIs are not significantly different between patients with MSI-high/dMMR *BRAF*^{V600E}-mutant and MSI-high/dMMR *BRAF* wild-type tumors.[113] Moreover, a recent post hoc analysis confirmed that survival and safety outcomes among Asian patients in KEYNOTE-177 were consistent with the primary analysis population.[114]

Although ORR was improved with first-line pembrolizumab versus standard chemotherapy in KEYNOTE-177 (45.1% vs. 33.1%),[111] pembrolizumab has not been directly compared with more intensive regimens such as FOLFOXIRI plus bevacizumab, which has an estimated ORR of 64.5% in patients with mCRC.[58] Thus, for selected patients with very bulky or symptomatic MSI-high mCRC, upfront intensive chemotherapy may be considered a first-line treatment. This may be particularly relevant in patients with extensive liver metastases, which are increasingly recognized as ICI-resistant sites in mCRC. In a recent cohort study of first-line pembrolizumab in dMMR mCRC, ORR was 21% among patients with liver metastasis versus 63% in those with non-liver metastases.[115]

7.2 | Second-line therapy

There is a lack of randomized data to guide treatment decisions for patients whose disease has progressed after first-line immunotherapy. Both targeted therapy and chemotherapy represent appropriate options for immunotherapy-refractory patients, but the most beneficial way to sequence these is currently unclear (Figure 1).

In patients with MSI-high/dMMR mCRC who received first-line chemotherapy rather than pembrolizumab, nivolumab plus ipilimumab is a recommended second-line treatment option.[17,41] This guidance is based on data from the Phase 2 CheckMate 142 trial, which evaluated nivolumab monotherapy and nivolumab/ipilimumab in patients who had progressed after ≥1 prior line of systemic treatment.[107,108,116] Both treatments were associated with high rates of response and disease control for ≥12 weeks, and comparable efficacy results were reported in patients with *BRAF*-mutant mCRC.[107,108,116] As an alternative to second-line nivolumab/ipilimumab, pembrolizumab may also be considered after first-line chemotherapy, based on efficacy data from the single-arm, Phase 2 KEYNOTE-164 trial.[117]

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8 | MONITORING RECOMMENDATIONS FOR *BRAF*^{V600E}-MUTANT mCRC

For patients with mCRC receiving active treatment, European guidelines recommend that radiological evaluation (viz., computed tomography [CT]) should be carried out every 8–12 weeks, in addition to measurement of carcinoembryonic antigen (CEA) levels.[17] Although Pan-Asian guidelines suggest that a slightly longer interval may be more appropriate for managing patients with mCRC in general (i.e., at least every 12 weeks),[41] a recent European expert consensus panel agreed that the aggressive nature of *BRAF*^{V600E}-mutant mCRC warrants more frequent monitoring (i.e., at least every 2 months).[118] We agree that monitoring every 6–8 weeks is preferable to evaluate treatment response and ensure prompt intervention upon disease progression (consensus statement 7; Table 2); however, we also acknowledge that monitoring intervals should be optimized on a case-by-case basis. Serum tumor markers such as CEA and carcinoma antigen 19-9 may be helpful to detect early progression; however, they are not always elevated in patients with *BRAF*^{V600E}-mutant mCRC, particularly those with MSI-high disease.[119] Recent research has demonstrated the utility of circulating tumor DNA (ctDNA) and plasma mutant allele fractions as surrogate markers of tumor burden in mCRC,[120,121] and these liquid biopsy technologies could inform monitoring and management decisions in the future.

CT is a widely available and cost-effective method to routinely monitor patients with mCRC; however, it should be noted that peritoneal metastases are difficult to detect using this imaging modality.[122] Therefore, in patients with suspected disease not visible on CT alone, we recommend supplementing CT with additional imaging modalities where available (e.g., positron emission tomography [PET] and magnetic resonance imaging [MRI]).

9 | MANAGEMENT OF OLIGOMETASTATIC *BRAF*^{V600E}-MUTANT mCRC

Current clinical guidelines recommend that local treatment, including surgical resection and ablative therapies, should be considered for the management of oligometastatic disease in patients with mCRC.[17,41,44] Decisions regarding local treatment should be discussed within a multidisciplinary team of experts, guided by imaging (e.g., thorax, abdomen, and pelvis CT, MRI, ultrasound, PET), and should take disease-, treatment-, and patient-related factors into account (e.g., size, number, and location of metastases, likelihood of complete eradication with local treatment, local expertise, patient frailty, and preferences). Induction chemotherapy is typically recommended before local treatment, particularly in those with initially unresectable metastases, as it may increase the likelihood of subsequent resection (i.e., conversion chemotherapy).[17,123] For patients with resectable oligometastatic disease (e.g., colorectal liver metastasis), surgery remains the standard of care; however, thermal ablation or stereotactic body radiotherapy can be considered for small liver metastases.[17,41,44,124] For patients with limited peritoneal metastasis, complete cytoreductive surgery (CRS) can be considered.[17,41,44] The survival benefit of adding hyperthermic intraperitoneal chemotherapy (HIPEC) to CRS for colorectal peritoneal metastases has not been demonstrated in a randomized trial and should not be considered a standard treatment approach.[125,126]

Although *BRAF*^{V600E}-mutant mCRC is associated with poor prognosis overall, there is mixed evidence that outcomes following local treatment may be worse in patients with *BRAF*^{V600E}-mutant mCRC. For example, a retrospective cohort analysis of patients who underwent resection for colorectal liver metastasis ($n = 853$, including 43 patients with *BRAF*^{V600E}-mutant mCRC) found that the *BRAF*^{V600E} mutation was associated with significantly worse OS (HR: 2.76; $p < 0.001$) and disease-free survival (HR: 2.04; $p = 0.002$) versus *BRAF* wild-type.[127] Conversely, in an Australian retrospective study of patients who underwent metastasectomy of various sites, including liver, lung, and peritoneum ($n = 513$, including 30 patients with *BRAF*-mutant mCRC), median recurrence-free survival was not significantly different between *BRAF*-mutant and *BRAF* wild-type groups (16.0 vs. 19.4 months; $p = 0.10$), and differences in OS were not statistically significant in multivariate analyses (HR: 1.39; $p = 0.24$).[128] In the same study, an analysis of 158 patients with *BRAF*^{V600E}-mutant mCRC found that OS was significantly improved in patients who underwent metastasectomy compared with those who did not (HR: 0.34; $p = 0.001$).[128] This is consistent with another retrospective study that reported significantly improved OS among patients with *BRAF*^{V600E}-mutant mCRC who underwent resection of isolated liver metastases versus unresected patients (median OS: 34.0 vs. 10.6 months; $p < 0.0001$).[129]

Several retrospective studies have reported that CRS/HIPEC for colorectal peritoneal metastases is associated with worse survival outcomes in patients with *BRAF*^{V600E}-mutant versus *BRAF* wild-type mCRC.[130–132] Conversely, a large retrospective study of 174 patients who underwent CRS/HIPEC for colorectal peritoneal metastasis (including 43 patients with *BRAF*^{V600E}-mutant mCRC) found that OS and disease-free survival were not significantly different between patients with *BRAF*-mutant, *KRAS*-mutant, and double wild-type cases.[133]

A recent randomized trial has demonstrated improved OS from the addition of liver transplant to standard chemotherapy in patients who have mCRC, unresectable liver metastases, no extrahepatic disease, and who have responded to chemotherapy for at least three months.[134] However, patients with *BRAF*^{V600E} mutations were excluded from the study, and therefore this cannot be considered a standard treatment option for this group.

Based on current evidence, we agree with clinical guidance that patients with *BRAF*^{V600E}-mutant mCRC should not be excluded from local treatments for metastatic disease sites if they are otherwise suitable candidates.[17] However, we reiterate the importance of meticulous staging to ensure that disease is truly localized, initial systemic therapy to test tumor biology, and multidisciplinary team review to carefully select only those patients most likely to benefit from aggressive treatment (consensus statement 8; Table 2).

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10 | FUTURE DIRECTIONS

Following the success of the BEACON CRC trial,[68,69] several studies are investigating whether encorafenib/cetuximab plus other therapies may further improve outcomes for patients with *BRAF*^{V600E}-mutant mCRC. The ongoing Phase 3 BREAKWATER trial will evaluate encorafenib/cetuximab with or without chemotherapy for the first-line treatment of MSS *BRAF*^{V600E}-mutant mCRC.[135,136] In the safety-lead in component of BREAKWATER, patients who had received ≤1 prior systemic therapy received either encorafenib/cetuximab plus FOLFOX ($n = 27$) or encorafenib/cetuximab plus FOLFIRI ($n = 30$) until disease progression or unacceptable toxicity.[137,138] Both regimens were generally tolerable; median PFS and ORR were 11.1 months and 68.4%, respectively, in patients receiving first-line encorafenib/cetuximab plus FOLFOX, compared with non-estimable PFS and ORR 75.0% in those receiving first-line encorafenib/cetuximab plus FOLFIRI.[136] Based on these safety lead-in results, the Phase 3 component of BREAKWATER will evaluate first-line encorafenib/cetuximab with or without FOLFOX versus investigators' choice of chemotherapy (i.e., FOLFOX, FOLFOXIRI, or CAPOX, each with or without bevacizumab), and a third cohort will be enrolled to evaluate first-line encorafenib/cetuximab plus FOLFIRI versus FOLFIRI with or without bevacizumab.[135,136]

Another key area of research includes assessing the efficacy of encorafenib/cetuximab combined with PD-1 inhibition. First, in patients with MSI-high/dMMR *BRAF*^{V600E}-mutant mCRC, the Phase 2 SEAMARK trial will evaluate first-line combination therapy of encorafenib/cetuximab plus pembrolizumab, compared with standard first-line pembrolizumab monotherapy.[139,140] Patient enrolment into SEAMARK commenced in July 2022, and study completion is expected in March 2027.[139,140] Additionally, a similar strategy is being explored, specifically in MSS patients. MSS CRC tumors have typically been considered "immune-cold" and unlikely to respond to single-agent PD-1 inhibition.[141] However, based on the hypothesis that targeted BRAF and EGFR inhibition may reduce MMR gene expression, promote the MSI-high phenotype, and subsequently increase response to immunotherapy, the Phase 2 Southwest Oncology Group S2107 study will evaluate encorafenib/cetuximab with or without nivolumab in patients with MSS *BRAF*^{V600E}-mutant mCRC who have previously received 1–2 prior lines of chemotherapy.[142,143]

Wee1 is a protein kinase that regulates the G_2 checkpoint of the cell cycle and arrests mitosis in response to DNA damage.[144] Based on the hypothesis that Wee1 blockade may increase the effectiveness of DNA-damaging agents by overriding the G_2 checkpoint and inducing cell death through mitotic catastrophe, several studies are investigating Wee1 inhibitors for the treatment of cancer.[144] In particular, an ongoing Phase 1/2 trial (NCT05743036) will assess the safety, tolerability, and potential clinical benefit of adding azenosertib to encorafenib/cetuximab in patients with *BRAF*^{V600E}-mutant mCRC who have previously received 1–2 prior lines of systemic therapy.[145]

As previously mentioned, many patients develop resistance to targeted therapies through genomic alterations in the MAPK pathway; therefore, several studies have explored mechanisms of acquired resistance and therapeutic targets to circumvent MAPK reactivation in *BRAF*^{V600E}-mutant mCRC.[99–102,146] Recent ctDNA analyses found that *KRAS* and *NRAS* mutations, *MET* amplification, and *MAP2K1* mutations were commonly acquired among patients receiving encorafenib/cetuximab with or without binimetinib in BEACON CRC.[99] To overcome acquired mutations that confer treatment resistance, several agents targeting the MAPK pathway have been developed and investigated in Phase 1 trials of *BRAF*-mutant cancers, including ulixertinib (ERK1/2 inhibitor), LY3009120 (pan-RAF inhibitor), and lifirafenib (RAF dimer inhibitor).[147–149] Based on preclinical data that the protein tyrosine phosphatase SHP2 mediates acquired resistance in ERK-dependent tumors,[150] an ongoing Phase 1b study will evaluate TNO155 (SHP2 inhibitor) plus dabrafenib (BRAF inhibitor) and either trametinib (MEK inhibitor) or LTT462 (ERK inhibitor) in patients with *BRAF*^{V600E}-mutant mCRC.[146,151]

11 | CONCLUSIONS

Patients with *BRAF*^{V600E}-mutant mCRC have a particularly poor prognosis; however, increased understanding of the molecular landscape of CRC has expanded the treatment options available to this population. In light of these advances, an Asia-Pacific expert panel developed evidence-based consensus statements to guide the diagnosis, treatment, and management of *BRAF*^{V600E}-mutant mCRC in this region. For patients with MSS *BRAF*^{V600E}-mutant mCRC, doublet chemotherapy plus bevacizumab is the preferred first-line treatment strategy, followed by second-line encorafenib/cetuximab. For patients with MSI-high *BRAF*^{V600E}-mutant mCRC, first-line immunotherapy with pembrolizumab is the current standard of care. Molecular testing at diagnosis is critical to ensure that all patients follow the most efficacious treatment pathway for their mCRC subtype, and close monitoring is important to ensure prompt intervention upon disease progression. The BEACON CRC trial led to a significant paradigm shift towards targeted therapies for *BRAF*^{V600E}-mutant mCRC; therefore, we keenly await the results of ongoing studies that may provide additional treatment options and further improve survival outcomes for patients in our region.

AUTHOR CONTRIBUTIONS

Oliver Piercey and Jayesh Desai co-chaired the expert consensus meetings and conceptualized draft consensus statements based on the meeting discussions. All authors participated in the expert consensus meetings, refined and voted on the consensus statements, participated in the drafting and critical review of the manuscript, and gave final approval of the version to be published.

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in the expert consensus meetings, nor in the development of the consensus statements and subsequent publication.

CONFLICT OF INTEREST STATEMENT

Oliver Piercey reports speaker fees from Bristol Myers Squibb. Lorraine Chantrill has served on advisory boards for Amgen, AstraZeneca, Bristol Myers Squibb, Eisai, and Merck and reports speaker fees from AstraZeneca and Pierre Fabre. Hung-Chih Hsu and Timothy Price have no conflicts of interest to disclose. Brigette Ma has served on advisory boards for Merck Serono and MSD; reports speaker fees from AstraZeneca and Merck Serono; and reports research funding from the Hong Kong Health and Medical Research Fund (grant number 6905168) and Merck Serono. Iain Beehuat Tan has served on advisory boards for Amgen, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Guardant Health, Merck Serono, MSD, Natera, Novartis, Pierre Fabre, and Roche; and reports research funding from MSD, Roche, and Taiho. Hao-Wei Teng has served on advisory boards and reports speaker fees from Amgen, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Foundation Medicine, Merck, MSD, Pfizer, Pierre Fabre, Roche, and TTY Biopharm; and reports research funding from Bayer. Jeanne Tie has served on advisory boards for AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Illumina, MSD, Pierre Fabre, Roche, and Takeda; has served as a consultant for Haystack Oncology; and reports speaker fees from Amgen and Servier. Jayesh Desai has served as a consultant and as an advisory board or steering committee member for Amgen, Axelia, Bayer, BeiGene, Boehringer Ingelheim, Daiichi Sankyo, Ellipses, GSK, IQVIA, Merck KGaA, Novartis, Pfizer, Pierre Fabre, and Roche/Genentech; and reports institutional research funding from Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb, GSK, Novartis, and Roche/Genentech.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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