Third- or Later-line Therapy for Metastatic Colorectal Cancer: Reviewing Best Practice

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Abstract

An increasing number of patients with metastatic colorectal cancer (mCRC) are able to receive 3 or more lines of therapy. Treatments in this setting can include regorafenib (an oral multikinase inhibitor), trifluridine/tipiracil hydrochloride (TAS-102), antibodies that target epidermal growth factor receptor for patients with RAS wild-type tumors (if no prior exposure), and, where approved, anti-programmed cell death protein 1 inhibitors for patients with microsatellite instability-high mCRC. Although guidelines describe the available treatment options, few insights are provided to guide selection and sequencing. In this article, we share expert opinion from diverse geographic regions, to offer guidance for best practice when selecting and managing third-line treatment for mCRC. Various factors, including performance status, age, and tumor sidedness, can be used to guide treatment selection. Biomarkers, such as *RAS*, *BRAF*, and microsatellite instability, can be useful for treatment stratification. Management of adverse events, to maintain quality of life, is a key consideration and is crucial to best practice in this setting. Common toxicities associated with third-line treatments are hand-foot skin reaction, fatigue, diarrhea, and cytopenias. Patients who receive third-line and later-line treatments should be monitored for these events, especially during the first 2 cycles. Dose modifications can also be used to manage toxicities and to minimize the effect on quality of life, while maximizing treatment benefit. Clinical trials of emerging agents, new treatment combinations, and novel therapies continue the efforts to improve outcomes for patients with mCRC. Sharing expert opinions on best practice for treatment selection and management can ultimately improve outcomes for patients with mCRC.

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Introduction

Overall survival (OS) in patients with metastatic colorectal cancer (mCRC) has been improving over the past 2 decades, and the median has now reached more than 30 months.[1-4] This increase has been driven by several factors, including improvements to first-line treatments and their strategic use, and an increase in available options.[2-4]

First-line and second-line treatment options for patients with mCRC include doublet or triplet chemotherapy plus a targeted biologic, such as an anti-angiogenic or, in patients with *RAS* wild-

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type (WT) disease, an epidermal growth factor receptor (EGFR) inhibitor.[4-6]

In the third-line and later-line setting, regorafenib and trifluridine/tipiracil are available for patients with mCRC[4-6] whose disease has progressed despite treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (anti-VEGF) therapy and, if *RAS* WT, an anti-EGFR therapy, or who have contraindications to these treatments[7,8] (Table 1 and Table 2). Regorafenib is an oral multikinase inhibitor that was approved by the United States (US) Food and Drug Administration (FDA) in 2012[7] and by the European Medicines Agency (EMA) in 2013,[24] and has since been made available in several other countries worldwide, including Japan. The combination of trifluridine and tipiracil hydrochloride (TAS-102) is orally administered[25] and was approved in Japan in 2014,[26] in the US in September 2015,[8] and in Europe in 2016.[27]

The anti-programmed cell death protein 1 (anti-PD-1) immune checkpoint inhibitors pembrolizumab and nivolumab were approved in the US by the FDA in 2017, and nivolumab plus ipilimumab was approved by the FDA in 2018,[28] all in the second- and later-line setting for patients with microsatellite instability-high (MSI-H) or deficient DNA mismatch repair mCRC whose disease has progressed despite treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (Table 3).[29,31-33] At present (October 2018), these agents are not approved for patients with MSI-H mCRC in Europe and Japan.

Advances in the molecular profiling of tumors have resulted in the identification of new targets and combination therapies. Of these, *ERBB2* amplification has emerged as a therapeutic target for the 3.0% to 5.0% of patients who have CRC with this molecular abnormality.[34] Combination therapy using the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab plus the dual EGFR/HER2 kinase inhibitor lapatinib,[35] or trastuzumab plus the HER2 dimerization inhibitor pertuzumab, has shown promising clinical benefit.[36]

As many patients are now receiving at least 3 lines of therapy,[2] a strategy for treatment in this setting, with goals including appropriate sequencing, is needed. Therefore, it is important to share expert opinions on best practice for using the different treatment options that are available. In this review, we share recommendations and insights on selecting and managing treatment of mCRC in the third-line or later-line setting from a panel of experts. The expert panel that authored this review represents a variety of regions, and their guidance reflects clinical and real-world evidence.

Selecting Treatment for mCRC in the Third-line Setting

The European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines both outline the treatment options available for patients with mCRC in the third-line setting and recommend treatments based on molecular biomarkers. However, few insights are offered to guide the selection and sequencing of treatments for this patient population.[4,5] In the absence of recommendations for treatment selection, sharing expert opinions can provide guidance for best practice to optimize third-line and later-line treatment of mCRC in the real world.

Patient Characteristics

Patient characteristics, such as performance status (PS), age, and comorbidities, as well as treatment goals and patients' preferences, are used to inform treatment selection for first-line therapy[4,5] and thus can also be applied to subsequent lines of therapy. In later-line settings, the number and class of previous therapies should also be considered. In the third-line setting, patient selection is an important indication of who will derive most benefit from systemic therapy, as there are currently no biomarkers that can predict which patients will benefit from regorafenib or trifluridine/tipiracil.

This expert panel agreed that patients with a low burden of disease or good PS typically tend to do well in the third-line and later-line settings. However, the panel recommended that PS, age, number and class of previous therapies, and patient's preference all be considered when deciding on a third-line treatment regimen. Adverse events from prior systemic therapies should also be considered, as such events can influence the choice of treatment. For example, patients with baseline cytopenias are more likely to receive regorafenib, whereas patients who experienced severe hand-foot skin reaction or fatigue are more likely to receive trifluridine/tipiracil. Comorbidities such as liver function should also be considered, as patients with a PS of 0 or 1 who have good liver function often derive long-term clinical benefit from regorafenib and trifluridine/tipiracil. Although patients with PS 2 at baseline may not be good candidates for regorafenib or trifluridine/tipiracil, patient age per se should not influence decisions on later-line treatment regimens.

These expert opinions are based on evidence from several clinical studies of regorafenib and trifluridine/tipiracil. In the CONSIGN (open-label phase 3b study of regorafenib in patients with mCRC; NCT01538680) study, patients treated with regorafenib who experienced a long progression-free survival (PFS) were more likely to have a more favorable baseline PS than those who had a short PFS.[37] Of those patients who achieved a PFS of $>$ 4 months, 58% were PS 0 at baseline and 41% were PS 1, whereas of those with PFS of $<$ 4 months, 44% were PS 0 at baseline and 56% were PS 1. A similar relationship was also observed in a real-world study (RECORA [regorafenib in patients with mCRC after failure of standard therapy; NCT01959269]), in which OS and PFS were shorter in patients with PS 2 than those with PS 0 or 1.[15] Median PFS was 3.6 months (95% confidence interval [CI], 3.1-5.0 months) in patients who were PS 0 at baseline compared with 2.5 months (95% CI, 1.9-2.9 months) in patients who were PS 2 ($P =$ .002). Poor PS unfavorably affected survival in a study nested in a compassionate-use program (REBECCA [REgorafeniB in mEtastatic Colorectal cancer in a French Compassionate Use progrAm; NCT02310477]).[14] PS did not seem to significantly influence the efficacy of trifluridine/tipiracil in the RECOURSE (retrospective cohort study of TAS-102 in patients with mCRC; NCT01607957) trial,[21,38] and trifluridine/tipiracil has shown efficacy in a clinical trial that included patients with a PS of 2.[39] Clinical trial results have also shown that mild-to-moderate hepatic or renal impairment does not affect the exposure of regorafenib.[7] Furthermore, although the prescribing information for trifluridine/tipiracil recommends considering the presence of comorbidities when selecting this

Table 1 Patient Outcomes in Clinical Trials and Real-world Studies of Regorafenib

Study	Study Location	No. Regorafenib-treated Patients	Median OS, mos (95% CI)	Median PFS, mos (95% CI)	Median Treatment Duration, mos	Patients With ≥ 1 Drug-related AE, n (%)	Patients With ≥ 1 Grade ≥ 3 Drug-related AE, n (%)
CORRECT[9,10]	Global	505	6.4 (NA)	1.9 (NA)	2.8	465 (93)	270 (54)
CONCUR[11]	Asia	136	8.8 (7.3-9.8)	3.2 (2.0-3.7)	2.4	132 (97)	74 (54)
CONSIGN[12]	Global	2864	NA	2.7 (2.6-2.7)	2.5	NA	NA (57)
CORRELATE[13]	Global	500[a]	NA	NA	2.4	NA (76)	NA (31)
REBECCA[14]	France	654	5.6	2.7	2.2	524 (80)	288 (44)[b]
RECORA[15]	Germany	458	5.6 (5.2-6.6)	3.2 (2.9-3.5)	NA	288 (63)	77 (17)
Kopeckova et al, 2017[16]	Czech Republic	148	9.3 (5.6-13.0)	3.5 (2.7-4.2)	2.9	NA	5 (3)[c]
Calcagno et al, 2016[17]	France	29	6 (5-8)	NA	2.5	25 (86)	NA
Xu et al, 2018[18]	Korea	32	NR	4.2 (3.1-5.2)	NA	NA	12 (38)
Japan PMS[19]	Japan	787	7.0 (6.3-7.8)	NA	NA	702 (89)	NA
REGOTAS[20]	Japan	223	7.9 (6.8-9.2)	2.1 (2.0-2.4)	NA	NA	Hematologic: 30 (13)
							Nonhematologic: 104 (47)

Abbreviations: AE = adverse event; CI = confidence interval; NA = not available; NR = not reached; OS = overall survival; PFS = progression-free survival; PMS = post-marketing surveillance.
[a]Interim analysis.
[b]Of 512 patients among whom data on worst grade was available.
[c]Any AEs (not specifically drug-related).

Table 2 Patient Outcomes in Clinical Trials and Real-world Studies of Trifluridine/tipiracil

Study	Location	No. Trifluridine/ Tipiracil-treated Patients	Median OS, mos (95% CI)	Median PFS, mos (95% CI)	Patients With ≥ 1 Drug-related AE, n (%)	Patients With ≥ 1 Drug-related Grade ≥ 3 AE, n (%)
RECOURSE[21]	Multinational	534	7.1 (6.5-7.8)	2.0 (1.9-2.1)	524 (98)	370 (69)
TERRA[18]	Asia	406	7.8 (NA)	2.0 (NA)	NA	NA
Compassionate use Program[22]	Global	879	NA	NA	NA	NA
Japan PMS study[23]	Japan	3420	NA	NA	219 (6)[a]	NA
REGOTAS[20]	Japan	327	7.4 (6.6-8.3)	2.1 (2.0-2.3)	NA	Hematologic: 128 (39)
						Nonhematologic: 41 (13)

Abbreviations: AE = adverse event; CI = confidence interval; NA = not available; OS = overall survival; PFS = progression-free survival; PMS = post-marketing surveillance.
[a]Spontaneous reports of trifluridine/tipiracil adverse drug reactions by attending physicians.

treatment,[8] real-world findings suggest that mild-to-moderate hepatic or renal impairment does not seem to affect survival.[40] Finally, clinical data suggest that patient age does not affect the clinical benefit from either regorafenib or trifluridine/tipiracil.[38,41,42] In the CONSIGN trial of regorafenib, 78% of patients were < 70 years of age and 22% were ≥ 70 years of age. A subgroup analysis by age showed that median PFS was similar across the age groups. In patients < 70 years of age, the median PFS was 2.7 months (95% CI, 2.6-2.8 months) and 2.5 months (95% CI, 2.3-2.7 months) in those ≥ 70 years of age.[41] The dose received, duration of treatment, and rates of treatment modifications, as well as the safety profile, were also generally comparable between age groups.

The expert panel agreed that patients who have not previously received bevacizumab may derive greater benefit from regorafenib than those who have received prior bevacizumab therapy. This is supported by clinical study results that have shown that the benefit of treatment with regorafenib and trifluridine/tipiracil may increase with fewer prior therapies.[9,11,43] The REVERCE (randomised phase 2 study of regorafenib followed by cetuximab versus the reverse sequence in patients with mCRC; UMIN000011294) study compared the efficacy and safety of regorafenib followed by cetuximab versus cetuximab followed by regorafenib. The results from this study showed that patients who received regorafenib followed by cetuximab experienced longer PFS with second treatment (PFS2; 5.2 vs. 1.8 months; hazard ratio [HR], 0.29) and OS (17.4 vs. 11.6 months; HR, 0.61; $P = .03$) than those who received cetuximab prior to regorafenib.[44]

Currently, it is unclear how PS, age, and comorbidities may affect the response to nivolumab, nivolumab plus ipilimumab or pembrolizumab in patients with MSI-H CRC. Although subanalyses may provide some indication, the clinical trials did not enroll patients with a PS of 2, and few patients ≥ 65 years of age were included.[29,31] Therefore, it would be of interest to understand the response to nivolumab, nivolumab plus ipilimumab or pembrolizumab in older patients with MSI-H CRC and those with PS 2.

Molecular Biomarkers

Several biomarkers are used to inform treatment selection and understand the prognosis for patients with mCRC; the most common are *RAS* (*KRAS* and *NRAS* exons 2, 3, and 4), *BRAF*, and MSI; *HER2* is an emerging target.[34,45] None of these molecular markers have been associated with response to regorafenib or trifluridine/tipiracil.[46-48]

This expert panel recommended that biomarkers are tested at diagnosis and should include *RAS, BRAF,* and MSI. Although some experts also recommend testing for *HER2* at diagnosis, the expert from France feels the evidence is not clear for HER2 testing at diagnosis. The presence of *RAS* mutations excludes the use of EGFR inhibitors, such as cetuximab and panitumumab, as patients with such mutations do not derive benefit from these agents and they may have a detrimental effect. The expert panel also agreed that a BRAF V600E mutation suggests using FOLFOXIRI (5-flourouracil, leucovorin, oxaliplatin, and irinotecan)/bevacizumab as first-line treatment, followed by a clinical trial, or an EGFR inhibitor in combination with a MEK inhibitor and a BRAF inhibitor, if available. *HER2* positivity suggests delaying the use of an EGFR inhibitor and enrolling the patient in a clinical trial or, if

Table 3 Outcomes with Nivolumab and Pembrolizumab in Patients With MSI-H mCRC

	Location	Number of Patients	ORR, % (95% CI)	DCR, % (95% CI)	Patients With ≥ 1 Drug-related AE, %	Patients With ≥ 1 Drug-related Grade ≥ 3 AE, %
Nivolumab[29]	Global	74	31.1 (20.8-42.9)	69 (57-79)	49	20
Nivolumab+ ipilimumab[30]	Global	119	55 (45.2-63.8)	80		32
Pembrolizumab[31]	Global	61	26.2 (15.8-39.1)	50.8 (37.7-63.9)	Not specified	Not specified

Abbreviations: AE = adverse event; DCR = disease control rate (≥ 12 weeks); ORR = overall response rate.

available off-trial, initiating dual HER2 blockade. MSI-H positivity suggests that the approved PD-1 inhibitors (nivolumab and pembrolizumab)[32,33] should be used in the second-line or later-line settings in the US,[49] although these immunotherapies remain investigational in Europe, so MSI status testing is used to assist in genetic counseling.[4]

Studies investigating novel biomarkers, such as carbohydrate antigen-19, CCL5/CCR5 pathway genes, and DNA repair-related genes, for regorafenib and trifluridine/tipiracil are ongoing.[50-53] A biomarker for these treatments would be valuable for informing patient selection and may improve patient quality of life by avoiding exposure to unnecessary toxicities. Molecular classification of individual CRC tumors through the consensus molecular subtypes[54] remains investigational, and the effect on clinical practice is unclear.

Tumor Sidedness

Tumor sidedness is an important prognostic factor in mCRC, as tumors that originate on the right are associated with poorer outcomes than those originating on the left side.[43] Furthermore, sidedness may also be predictive of response to treatment in the first-line setting; greater benefit from treatment with an anti-EGFR therapy was observed in patients with *RAS* WT disease who had left-sided tumors than in patients with right-sided tumors.[43] Indeed, bevacizumab plus chemotherapy may provide greater clinical benefit than anti-EGFR therapies in patients with right-sided tumors.[55]

This expert panel agreed that tumor sidedness does not seem to affect response to regorafenib or trifluridine/tipiracil in the third-line setting. Some members of the panel advised that they do not usually use anti-EGFR therapies in patients with right-sided tumors, including those with RAS WT disease, but do use these treatments in patients with left-sided tumors. These experts expressed a preference for bevacizumab for the treatment of patients with right-sided tumors in the first-line setting. Other panel members suggested that triplet chemotherapy plus an EGFR inhibitor or plus bevacizumab are also treatment options for left-sided and right-sided tumors, respectively. A sub-analysis of the CORRELATE (prospective observational trial of regorafenib in mCRC; NCT01843400) study showed that tumor sidedness did not affect response to regorafenib, as OS was similar for right-sided and left-sided tumors; 6.3 and 6.7 months, respectively ($P = .278$).[13] Similarly, an analysis of both regorafenib and trifluridine/tipiracil found that time to treatment failure and OS were unaffected by tumor location.[56]

Although nivolumab, nivolumab plus ipilimumab and pembrolizumab are available in later-line settings for patients with MSI-H mCRC, the effect of tumor sidedness on response to these treatments has not yet been assessed. MSI has been associated with right-sidedness and a poor response to EGFR-targeted therapies,[5,57] but further evidence is needed before this association can be translated into clinical practice.

Managing Third-line Treatment for mCRC

Prevention and Management of Adverse Events (AEs)

Maintaining quality of life is an essential goal for third-line and later-line treatments for patients with mCRC. The prevention and management of AEs are key factors in achieving this goal and so are crucial to best practice for management of this patient population.

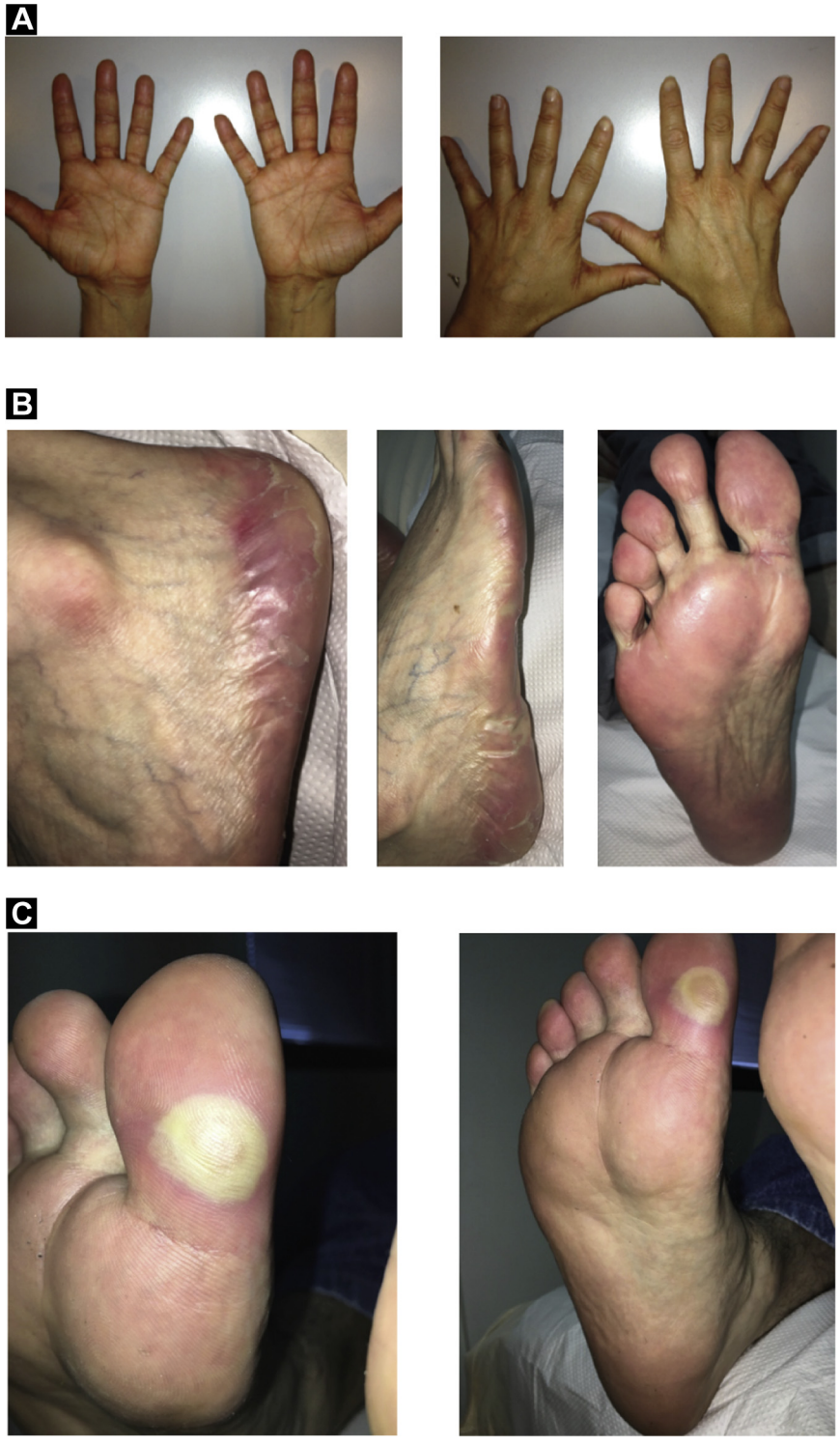
The most common regorafenib-related AEs observed in clinical studies were hand-foot skin reaction, fatigue, diarrhea, and hypertension.[12] These AEs tend to emerge early and attenuate over time, even when dosage is maintained.[10-12] The most common trifluridine/tipiracil-related AEs in clinical trials were hematologic, nausea/vomiting, diarrhea, decreased appetite, and fatigue.[21] Immune checkpoint inhibitor therapies, such as pembrolizumab and nivolumab, are associated with immune-mediated reactions and infusion-related reactions.[32,33] It is unclear whether there are any nuances in the AE profiles of pembrolizumab and nivolumab in patients with MSI-H mCRC compared with other tumor types. A recent study of cobimetinib plus atezolizumab, atezolizumab alone, and regorafenib in patients with microsatellite stable CRC, which did not meet the primary endpoint, showed that treatment-related AEs of any grade with $>$ 30% occurrence were diarrhea (56%), rash (42%), and nausea (32%) with combination therapy and none with atezolizumab monotherapy.[58]

This expert panel agreed that early onset of hand-foot skin reaction (Figure 1) in response to regorafenib treatment may be associated with duration of OS. However, hand-foot skin reaction is one of the most common reasons for treatment discontinuation, so careful management is important. The expert panel agreed that healthcare professionals need to be well-informed about the risks for, and management of, hand-foot skin reaction during long-term treatment with regorafenib. In the CORRECT (patients with mCRC treated with regorafenib or placebo after failure of standard therapy; NCT01103323) study, hand-foot skin reactions of any grade occurred in 47% of patients who received regorafenib, compared with 8% of those who received placebo, and of these 17% and $<$ 1%, respectively, were grade 3.[9] Hand-foot skin reactions associated with regorafenib typically manifest within 4 weeks of treatment initiation[9,10] and can negatively affect patient quality of life.[59] These reactions seem to be more common in Japanese patients (80%) than in non-Japanese patients (42%).[60] Guidance on the management of hand-foot skin reaction recommends maintaining skin moisture and integrity using emollients and creams. Urea (10%-40%) and salicylic acid (5%-10%) creams are also recommended, as keratolytics and topical analgesic gels can be used to relieve pain. Antiseptic baths, topical corticosteroids, antibiotics, and systemic pain relief can be added to the management regimen for higher grades of hand-foot skin reaction.[61]

Fatigue is a common symptom in advanced cancer, particularly in the third-line and later-line settings, as observed in the placebo arm of the CORRECT study,[9] and is often multifactorial. Fatigue can have a significant effect on quality of life, and there is no approved pharmacologic treatment to offer patients. Although clinical evidence suggests that medical prophylactic treatment with low-dose corticosteroids, such as dexamethasone 2 mg/day,[62] may reduce regorafenib-related fatigue, this expert panel also agreed that non-pharmacologic interventions, general supportive care, regular physical activity, and psycho-educational support, as well as rest and exercise,[63,64] may be beneficial for managing fatigue.

Fatigue of any grade occurred in 47% of patients who received regorafenib in the CORRECT study, compared with 28% of those who received placebo, with grade $\geq$ 3 events occurring in 10% and 5% of patients, respectively.[9] Hypothyroidism has been related to fatigue in patients receiving regorafenib and was easily reversed by

Figure 1 Images of Hand-Foot Skin Reactions (HSFRs). A, Grade 1 HFSR. Erythema and Mild Desquamation; B, Grade 2 HFSR. Painful Erythema, Desquamation, and Hyperkeratosis at Pressure Points; C, Grade 3 HFSR



Photos provided by Marcela Moreno and Juan M O'Connor, Dermatooncology, Instituto Fleming, Argentina.

Table 4 Expert Opinion on Monitoring Patients Receiving Third-line Therapies

Therapy	Events to Monitor	Monitoring Frequency
Regorafenib	Hand-foot skin reaction	Cycles 1 and 2: weekly or biweekly
	Skin rash	Subsequent cycles: monthly
	Fatigue	
	Diarrhea	
	Liver function	
	Blood pressure	
Trifluridine/tipiracil	Hematologic events (especially in patients with previous events)	Cycles 1 and 2: weekly or biweekly
		Subsequent cycles: monthly

L-T4 administration,[65] suggesting that routine assessment of thyroid function in patients with fatigue may be beneficial. However, additional evidence is needed before this is adopted as standard practice.

Diarrhea is associated with regorafenib treatment, and a long-lasting low-grade event can affect a patient's quality of life more than a grade 3 event of short duration. Diarrhea was common among patients receiving regorafenib in the CORRECT and GRID (Gastrointestinal stromal tumors - Regorafenib In progressive Disease; NCT01271712) studies.[7,9,66] In the CORRECT study, diarrhea of any grade occurred in 34% of patients who received regorafenib and 8% who received placebo, and of these, 7% and 1%, respectively, were grade 3.[9] This expert panel recommended patient education on the need to report and manage diarrhea. Patients who experience severe diarrhea may benefit from octreotide acetate, which provides rapid control and prevents severe dehydration.[67,68] Oral mucositis (stomatitis) has also been associated with regorafenib treatment, and the intensity may be influenced by patient age, dental hygiene, nutritional status, and associated infections. In the CORRECT and GRID studies of regorafenib, oral mucositis (stomatitis) was observed, usually at the end of the first week of treatment.[9,66] In the CORRECT study, oral mucositis of any grade occurred in 27% of patients who received regorafenib and 4% of patients who received placebo, with grade 3 events occurring in 3% and 0% of patients, respectively.[9] Preventative measures, such as good oral hygiene and dental care, for reducing the risk of this event are also recommended. Liver abnormalities can occur with regorafenib treatment and can be severe. Liver abnormalities were observed with regorafenib in the CORRECT study, including 1 case of fatal liver dysfunction.[9,66] As these abnormalities usually emerge soon after treatment initiation, this expert panel suggested carrying out liver function tests every 2 weeks during the first 2 cycles, and modifying treatment as needed, based on clinical practice guidelines.

The recent ReDOS (REgorafenib Dose Optimization Study; NCT02368886) study assessed a dose-escalation strategy that started regorafenib at 80 mg and escalated weekly (as toxicity allowed) to 160 mg, in comparison with the approved 160 mg starting dose. The dose-escalation strategy was found to be associated with lower rates of grade 3/4 toxicities, including hand-foot skin reaction, fatigue, and hypertension, than the approved 160 mg starting dose.[69] This allows the dosing of regorafenib to be optimized for individual patients.

Trifluridine/tipiracil is also associated with diarrhea. In the RECOURSE study, diarrhea of any grade was observed in 32% of patients who received trifluridine/tipiracil, compared with 12% who received placebo.[21] Trifluridine/tipiracil is also associated with nausea and vomiting; in the RECOURSE study, 48% of patients experienced nausea of any grade and 28% experienced vomiting of any grade, compared with 24% and 14%, respectively, in the placebo group.[21] As these events occur frequently, are common to many therapies, and can influence adherence,[70] it is important that they are managed effectively.

Results from the RECOURSE trial have also shown that treatment with trifluridine/tipiracil was associated with anemia (77%), leukopenia (77%), neutropenia (67%), and thrombocytopenia (42%) of any grade.[21] As these events occur frequently and can be serious, complete blood counts should be taken prior to initiating therapy and on day 15 of every cycle.[8] Trifluridine/tipiracil should only be initiated in patients with absolute neutrophil counts (ANCs) of $\geq 1500/mm^3$, any incidence of febrile neutropenia has resolved, platelet counts of $\geq 75{,}000/mm^3$ and any grade 3/4 nonhematologic AEs have resolved to grade 0 or 1. Furthermore, trifluridine/tipiracil should be withheld if ANCs are $< 500/mm^3$ or febrile neutropenia occurs, platelet counts are $< 50{,}000/mm^3$ and there are any grade 3/4 non-hematological AEs. Treatment with granulocyte-colony stimulating factor (G-CSF) has been shown to reduce the incidence of febrile neutropenia in the RECOURSE study, in which more patients who received trifluridine/tipiracil were treated with G-CSF than those who received placebo.[71]

Immune-mediated reactions are not uncommon in patients receiving treatment with immune checkpoint inhibitor therapies, although rates of life-threatening or fatal events are low.[29,31-33] Prompt recognition and management of immune-mediated events are crucial, and optimal management is dependent on the organ involved and the severity. Guidelines for identifying and managing immune-mediated events are currently available from ESMO,[72] American Society of Clinical Oncology (ASCO),[73] and NCCN,[74] and provide practical information, so their use is strongly advised. In most cases, immunotherapy should be suspended or discontinued (depending on the severity and organ system involved) in patients experiencing an AE of moderate (grade 2) or greater severity. This expert panel agreed that corticosteroids are the mainstay of treatment for patients experiencing severe or life-threatening toxicities; however, in cases of severe and steroid-refractory toxicity, infliximab or other immunosuppressive

Table 5 Expert Opinion on Dose Modification in the Third-Line Setting

Therapy	Approach
Regorafenib	Patients with poor PS: start at 80 mg or 120 mg and gradually increase or modify in response to benefit and tolerability
	Dosing should be suspended for any severe or life-threatening AEs (grade ≥ 3), symptomatic (grade ≥ 2) hypertension, or moderate (grade 2) hand-foot skin reaction that does not resolve within 1 week of dose reduction
	Treatment can be reintroduced at 80 mg or 120 mg once symptoms have resolved and the risk of event recurrence is mitigated
	Treatment should be discontinued if 80 mg is intolerable, or in cases of severe or life-threatening hepatotoxicity
Trifluridine/tipiracil	If hematologic AEs occur, a new cycle of treatment should not be started until the ANC ≥ 1500, platelets ≥ 75,000, and all severe (grade ≥ 3) nonhematologic AEs have resolved
	After recovery, treatment can be reintroduced at a dose 5 mg/m^2 lower in cases of febrile neutropenia, uncomplicated grade 4 neutropenia or thrombocytopenia resulting in more than 1-week delay in starting the next cycle, and severe (grade 3) nonhematologic side effects that cannot be adequately managed with supportive care

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; PS = performance status.

therapies may be beneficial. Endocrinopathies can be managed with hormone replacement and may not require treatment discontinuation or steroids. Management of immune-mediated events by an experienced multi-disciplinary team can help mitigate and prevent the most serious complications associated with immune therapies, helping to maintain patient quality of life.

Patient Monitoring

The toxicities associated with third-line and later-line therapies mean patient monitoring is needed[7,8,24,27] to minimize the impact of these on patient quality of life, as well as maximizing the benefit of treatment.

This expert panel agreed that patients should be monitored closely during treatment with regorafenib, for hand-foot skin reaction, skin rash, diarrhea, fatigue, and changes in liver function and blood pressure. Monitoring should be carried out weekly or biweekly during the first 2 cycles of treatment when these AEs occur most commonly, and monthly thereafter. Close monitoring is also recommended for patients receiving trifluridine/tipiracil and is particularly important for those who have experienced previous neutropenia, anemia, or thrombocytopenia (Table 4). These expert opinions are based on the prescribing information, clinical study data, and clinical practice guidelines, which state that regorafenib monitoring should be carried out weekly during the first 2 cycles of treatment and monthly thereafter,[75] with special attention to toxicities detected during prior cycles to prevent their worsening.[63,75,76] Similarly, trifluridine/tipiracil monitoring should be weekly or biweekly following treatment initiation.[8,27] Expert opinions from Korea and France describe a slightly different approach to patient monitoring in their clinics, with weekly follow-up only during the first cycle of treatment.

This panel agreed that monitoring of patients who are receiving nivolumab or pembrolizumab should closely follow the guidelines, with patients being monitored at each infusion and with increased frequency in cases of suspected toxicity.

Dose Modification

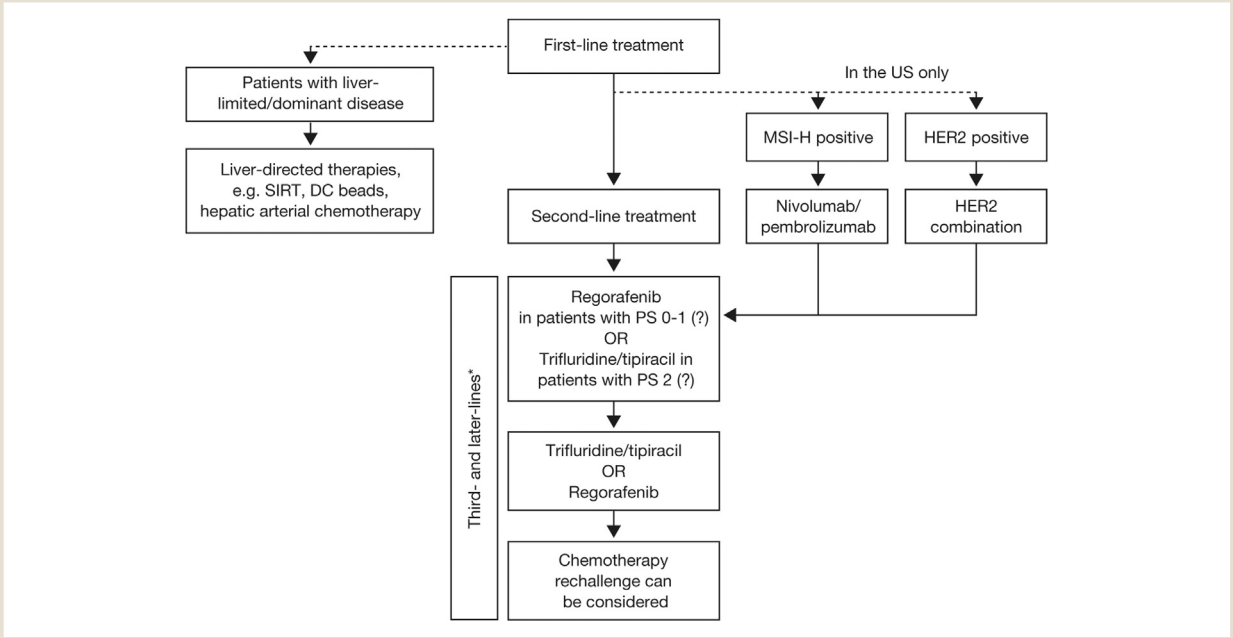
The licensed starting dose of regorafenib is 160 mg once-daily on a 3-weeks on/1-week off schedule.[7] The recommended starting dose of trifluridine/tipiracil is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) taken orally twice daily on day 1 to 5 and day 8 to 12 of each 28-day cycle.[8,27] The recommended starting dose for nivolumab is 240 mg every 2 weeks and for pembrolizumab is 200 mg every 3 weeks.[32,33] However, to maintain patient quality of life and maximize treatment benefit, dose modifications may be needed to address toxicities, such as hand-foot skin reaction, gastrointestinal AEs, fatigue, cytopenias, and immune-mediated reactions.[7,8,24,27,32,33]

The expert panel agreed that some prescribers are using alternatives to the standard regorafenib dosing schedule in some patients, such as those with poor PS scores. The regorafenib dose is gradually increased from a starting dose of 80 mg or 120 mg, depending on the clinical benefit and tolerability in each patient (Table 5), similar to the approach used in the ReDOS study.[69] However, the panel highlighted that alternatives to the 160 mg once daily on a 3-weeks on/1-week off schedule are not approved. The panel recommended that dose modifications of regorafenib and trifluridine/tipiracil are carried out based on the prescribing information (Table 5).[7,8,24,27]

Regorafenib should be suspended if a patient experiences any severe or life-threatening AEs (grade ≥ 3), symptomatic (grade ≥ 2) hypertension, or moderate (grade 2) hand-foot skin reaction that does not resolve within 1 week of dose reduction. Once symptoms have resolved and the risk of the event recurring has been mitigated, reintroducing regorafenib at a lower dose, such as 80 mg or 120 mg, should be considered. If hepatotoxicity occurs, treatment, even at a reduced dose, should be resumed with caution. Regorafenib should be discontinued if the patient is unable to tolerate the 80 mg dose, or in cases of severe or life-threatening hepatotoxicity. Clinical data have also shown that dose modifications or temporary discontinuation of therapy do not seem to negatively affect the efficacy of regorafenib.[9,11,14,77,78]

Results from the ReDOS study have shown that a significantly larger proportion of patients start a third cycle of regorafenib when the dose is escalated weekly from 80 mg to 120 mg and then to 160 mg over the cycle, compared with starting at 160 mg (43% vs. 25%; $P = .028$; including patients with disease progression before starting the third cycle).[69] In the Japanese phase II dose titration study (UMIN000018968), in which the starting dose of regorafenib was

Figure 2 Proposed Treatment Sequencing Strategy in Third-line and Later-lines for Patients With Metastatic Colorectal Cancer



Abbreviations: HER2 = Human Epidermal Growth Factor Receptor 2; MSI-H = microsatellite instability-high; PS = performance status; SIRT = selective internal radiation therapy. *Anti-EGFR therapies can be used in this setting, if not used previously (and as indicated). (?) Indicates this is a suggested approach.

120 mg, the disease control rate (36.7%) was comparable with results from the CORRECT trial (41%).[9,79] In addition to ReDOS, several ongoing clinical trials are currently investigating dose-escalation protocols for regorafenib, including REARRANGE (study comparing different dose approaches of induction treatment of regorafenib in mCRC; NCT02835924), the results from which are expected in 2019, and will be important for informing the optimal starting dose of regorafenib in clinical practice.

If hematologic AEs occur during treatment with trifluridine/tipiracil, a new cycle of treatment should not be started until the ANC $\geq$ 1500, platelets $\geq$ 75,000, and all severe (grade $\geq$ 3) nonhematologic AEs have resolved. Complete blood cell counts are advised on day 1 and day 15 of each cycle. Trifluridine/tipiracil should be suspended if ANC $<$ 500, febrile neutropenia occurs, platelets $<$ 50,000, and for all severe (grade $\geq$ 3) nonhematologic AEs. After recovery, reintroducing trifluridine/tipiracil at a dose that is 5 mg/m^2 lower is recommended in cases of febrile neutropenia, uncomplicated grade 4 neutropenia, or thrombocytopenia resulting in more than a 1-week delay in starting the next cycle, and severe (grade $\geq$ 3) nonhematologic AEs that cannot be adequately managed with supportive care, as described in the prescribing information.[8] In addition, G-CSF can be used as proactive supportive care in patients treated with trifluridine/tipiracil who experience neutropenia.[23]

This expert panel also recommended that treatment with nivolumab and pembrolizumab is suspended or permanently discontinued in patients who experience moderate, severe, or life-threatening toxicity, depending on the organ system involved and severity of the complications.

Clinical Markers of Response

The expert panel agreed that some class-effect events, such as arterial hypertension with regorafenib and myelosuppression with trifluridine/tipiracil, have been observed, but neither of these events seemed to indicate any clinical benefit. In addition, the expert panel agreed that the occurrence of hand-foot skin reaction and lung nodule cavitation may be predictors of long-term response to regorafenib. Changes such as density reduction in lung metastases, lung metastases cavitation, and longer time from first diagnosis to metastatic disease have been associated with favorable responses to regorafenib in clinical studies.[37,80,81] Such events may encourage clinicians and patients to persist with therapy, using dose adjustments to manage toxicities when necessary.[14,19,23,82-87] However, more evidence is required to determine whether such clinical responses could be used as robust markers that inform clinical decisions.

Several ongoing trials are investigating the use of imaging for the early identification of response to regorafenib (Kehagias et al, 2018[88]; NCT02175095 and JACCRO CC-12 [phase 2 study to evaluate the efficacy of regorafenib in mCRC patients by FDG-PET/CT; UMIN000015563]; TEXCAN [evaluation of treatment response with CHOI and RECIST criteria and CT texture analysis in patients with mCRC treated with regorafenib; NCT02699073]; KSCC1603 [retrospective cohort study for assessment of imaging changes after the use of regorafenib; UMIN000023329]), which would provide valuable additional evidence for confirming treatment response.

Treatment Sequencing

Appropriate treatment sequencing enables patients to receive all available agents, which is a key therapeutic goal in later-line settings.

Regorafenib and trifluridine/tipiracil should be considered for third-line or later-line therapy for patients with mCRC, where available and as indicated, along with nivolumab and pembrolizumab in eligible patient populations. However, treatment sequencing decisions can be challenging, and although NCCN guidelines recommend using nivolumab or pembrolizumab before regorafenib or trifluridine/tipiracil for patients with MSI-H mCRC, there is little other evidence to guide the sequencing of the different options. NCCN guidelines recommend sequential treatment with regorafenib and trifluridine/tipiracil, with the order of treatment at the discretion of the clinician; ESMO guidelines do not make any clear recommendations.[4-6]

Although there are no sequencing data from phase III studies, the expert panel agreed that regorafenib may provide more benefit when used earlier in the treatment paradigm. Furthermore, trifluridine/tipiracil is often well-tolerated, so may be more suitable as a later-line therapy and is equally effective whether patients have received regorafenib previously. The algorithm proposed in Figure 2 summarizes these expert opinions. In the RECOURSE study, the OS hazard ratio for patients who had received regorafenib prior to trifluridine/tipiracil and those who had not was 0.69 for both groups. There was no significant difference in OS between patients treated with trifluridine/tipiracil who had or had not previously received regorafenib.[21] Results from a further study in Japan showed that the median PFS in those who received regorafenib prior to trifluridine/tipiracil was 4.6 months, compared with 1.9 months in those who did not.[89] In addition, as described above in the REVERCE study, survival was longer for patients who received regorafenib followed by cetuximab than those who received cetuximab prior to regorafenib.[44]

Immunotherapies provide benefit but are limited to the small proportion (< 5%) of patients with MSI-H disease, in whom they are highly effective. Therefore, patients with MSI-H disease should be referred as expeditiously as possible to receive immune checkpoint inhibitors (Figure 2). Similarly, if patients have tumors with an *ERBB2* amplification (< 5% of cases) HER2-targeted combination therapy can be considered. There is only a low level of evidence for chemotherapy re-challenge, although further data are expected (Figure 2).

The expert panel recognized that many US clinicians use regorafenib following chemotherapy reintroduction; however, there is little evidence to support this strategy.[2] Indeed, no randomized study has addressed this question to date. Furthermore, the response to chemotherapy reintroduction can vary widely based on previous response to chemotherapy and the time since the prior treatment.[90] Results from clinical studies suggest that re-challenge with oxaliplatin may be suitable when no other treatment options are available, but it should be used with caution, as it can lead to additional toxicity[18,91,92] and is often not feasible because of residual peripheral neuropathy.[93] Some data are available that suggest that regorafenib may have a chemosensitizing effect, allowing re-challenge with chemotherapy after disease progression[92,94]; however, additional investigations into this effect are needed before expert guidance can be offered.

The plasticity of CRC cells and the dynamic clonal competition that takes place during EGFR-targeted therapy and on withdrawal of EGFR blockade might also be exploited in the clinic, as the decline of mutated RAS clones may renew the response to EGFR antibodies.[92,95,96] This observation provides a molecular rationale for studies that proposed re-challenge with cetuximab[97,98] or panitumumab[99,100] in patients with RAS WT disease after a previous response to anti-EGFR therapy. Additional studies investigating different re-challenge strategies using anti-EGFR therapies are ongoing and needed before integrating this approach into standard clinical practice.[92]

At present, the evidence suggesting the use of regorafenib earlier and trifluridine/tipiracil later in the treatment cycle is anecdotal. More data are required to determine the optimal sequencing of regorafenib and trifluridine/tipiracil as third-line or later-line therapy for mCRC, which will enable expert guidance to be provided and will assist with maximizing the benefit for patients.

Discussion

Current options for third-line and later-line treatment of patients with mCRC include regorafenib and trifluridine/tipiracil, and in patients with MSI-H mCRC, nivolumab, nivolumab plus ipilimumab, and pembrolizumab, where available. The expert opinions on best practice for treating patients with mCRC described here complement clinical guidelines and include consideration of patient characteristics, molecular biomarkers, and appropriate treatment sequencing, as well as effective management of AEs and dosing to optimize overall outcomes and improve quality of life. Best practice for treating patients with mCRC will continue to evolve as clinical trials of emerging agents, new treatment combinations, and novel therapies continue the efforts to improve outcomes for patients with mCRC.

Further clinical studies investigating the current treatment options are underway, as we continue to improve our understanding of the use of these therapies in the real world. In particular, nivolumab, nivolumab plus ipilimumab and pembrolizumab are in the early stages of use for patients with MSI-H mCRC and further studies are needed to understand best practice for using these agents. The use of re-challenge with anti-EGFR monoclonal antibodies has a biological rationale in the dynamic clonal competition of *RAS*-mutated cancer cells that takes place during previous EGFR-targeted therapy[95]; however, this approach should be confirmed in prospective trials that are ongoing. Furthermore, in patients with anti-EGFR antibody-naive mCRC, recent results from the REVERCE study,[44] which assessed the sequencing of regorafenib and cetuximab plus irinotecan, are interesting and may challenge current thinking on treatment sequencing, especially if this evaluation is repeated in a Western population. In addition, combination trials of regorafenib plus trifluridine/tipiracil (NCT03305913) and trifluridine/tipiracil plus bevacizumab (UMIN000012883, C-TASK FORCE [TAS-102 plus bevacizumab in patients with mCRC refractory to standard therapies])[101] are underway, and these results may also inform treatment sequencing.

Evaluation of immune checkpoint inhibitors in combination with currently available therapies and with other checkpoint inhibitors, for example nivolumab plus ipilimumab,[29] are ongoing, as such combinations are associated with survival benefits but can also be associated with higher levels of toxicity compared with monotherapy.[102] The results from such studies could inform treatment

selection and sequencing decisions and would need to be incorporated into best-practice recommendations for patients with mCRC.

New molecularly targeted combination therapies are also being investigated for third-line and later-line treatment, potentially offering a different approach to treatment for some patients with mCRC. The anti-HER2 antibody trastuzumab in combination with the dual EGFR/HER2 kinase inhibitor lapatinib has shown promise in the HERACLES (HER2 Amplification for Colo-rectaL cancer Enhanced Stratification study; EudraCT number 2012-002128-33) study, with an overall response rate of 30% in patients with *RAS* WT, HER2/neu-overexpressing mCRC.[103] Similarly, combination therapy using trastuzumab and pertuzumab has shown efficacy in the MyPathway phase IIa multiple basket study, in which 37 patients with *ERBB2*-amplified/HER2 overexpressed mCRC who had exhausted standard treatments were included and an overall response rate of 38% was achieved.[36] Ongoing studies are also evaluating the potential of combining pertuzumab with trastuzumab emtansine (T-DM1) in this patient population.[103] The highly selective HER2 tyrosine kinase inhibitor tucatinib is also being assessed in combination with trastuzumab in patients with HER2-positive CRC, as tumor inhibition has been observed in preclinical models.[104]

Several other novel agents are being investigated as third-line or later-line treatment options for mCRC.[3] Tyrosine kinase inhibitors, such as famitinib (NCT02390947), fruquintinib,[105] and anlotinib (NCT02332499), are under investigation in phase III trials. The alkylating agent temozolomide showed some activity in phase II studies of patients with mCRC and O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation,[106,107] even though molecular selection might be further improved leaving the latter approach under investigation.[108] The synergy between BRAF and EGFR inhibition in patients with *BRAF* mutations, as well as novel approaches such as the potential reversal of EGFR-inhibitor resistance with heat shock protein 90 and stem cell inhibitors, are also being assessed in ongoing research. Together, this wealth of active clinical research highlights the continuing efforts to improve quality of life and overall outcomes for patients with mCRC.

In conclusion, third-line and later-line treatment of mCRC requires a clear strategy to ensure patients receive maximum benefit while maintaining quality of life. Sharing current best practice approaches, based on expert guidance from several regions, as well as clinical and real-world evidence, can inform treatment decision-making and ultimately improve the overall management of patients with mCRC.

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