How I Treat

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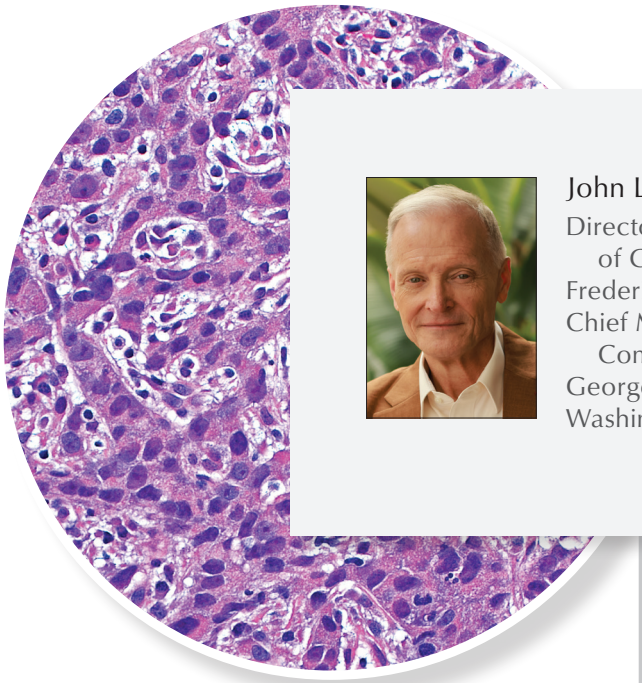
How I Treat mCRC in the Community: Think Chess, Not Checkers!



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How I Treat mCRC in the Community: Think Chess, Not Checkers!

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In the Clinic . . .

Consider the following patient cases encountered in my clinic.

Case 1: Indolent Disease, Long-Term Disease Control

A 59-year-old male was originally diagnosed with stage 2 colorectal cancer (CRC) 3 years ago. He did not receive adjuvant therapy. He then presented with small lung lesions and tested circulating tumor DNA (ctDNA)–positive. Molecular testing showed *RAS* wild-type, *BRAF* V600E wild-type, microsatellite-stable (MSS), and HER2-negative. Biopsy results were positive and the patient was considered unresectable.

As first-line therapy for metastatic CRC (mCRC), he received capecitabine and bevacizumab, which induced a response. At a 3-year follow-up, the patient remained asymptomatic, but several new lesions were detected, indicating progressive disease. After considering the available options, the patient was started on trifluridine/tipiracil plus bevacizumab and has had stable disease (SD) for 12 months.

Case 2: Balancing Tumor Response With Quality of Life

A 45-year-old female, working full time and married with 2 children, was diagnosed with recto-sigmoid colon cancer after developing rectal bleeding and narrowing of stool. A positron emission tomography (PET) scan detected liver and lung metastases. A multidisciplinary team considered the tumor not resectable. Molecular testing showed MSS, a *RAS* mutation, *BRAF* V600E wild-type, and HER2-negative.

Her induction treatment consisted of leucovorin, fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) plus bevacizumab, which induced a strong response by 6 cycles but with some neurologic toxicity. The oxaliplatin and irinotecan were discontinued, and capecitabine and bevacizumab were added. The patient's symptoms resolved and she returned to work and parenting duties. She received capecitabine/bevacizumab maintenance therapy for 9 months, then imaging revealed minor progressive disease. She had no change in bowel symptoms and no neuropathy. She was started on trifluridine/tipiracil plus bevacizumab and has had SD for 6 months.

Case 3: Molecularly Driven Treatment and Sequencing

A 72-year-old female presented with ascending colon cancer. Initial staging was negative. Surgery showed T3N2M1 with small peritoneal lesions. Molecular testing revealed a *BRAF* V600E mutation. A postoperative

On the Cover
Light micrograph of a poorly differentiated colon adenocarcinoma.

Credit: Ziad M. El-Zaatari/Science Source

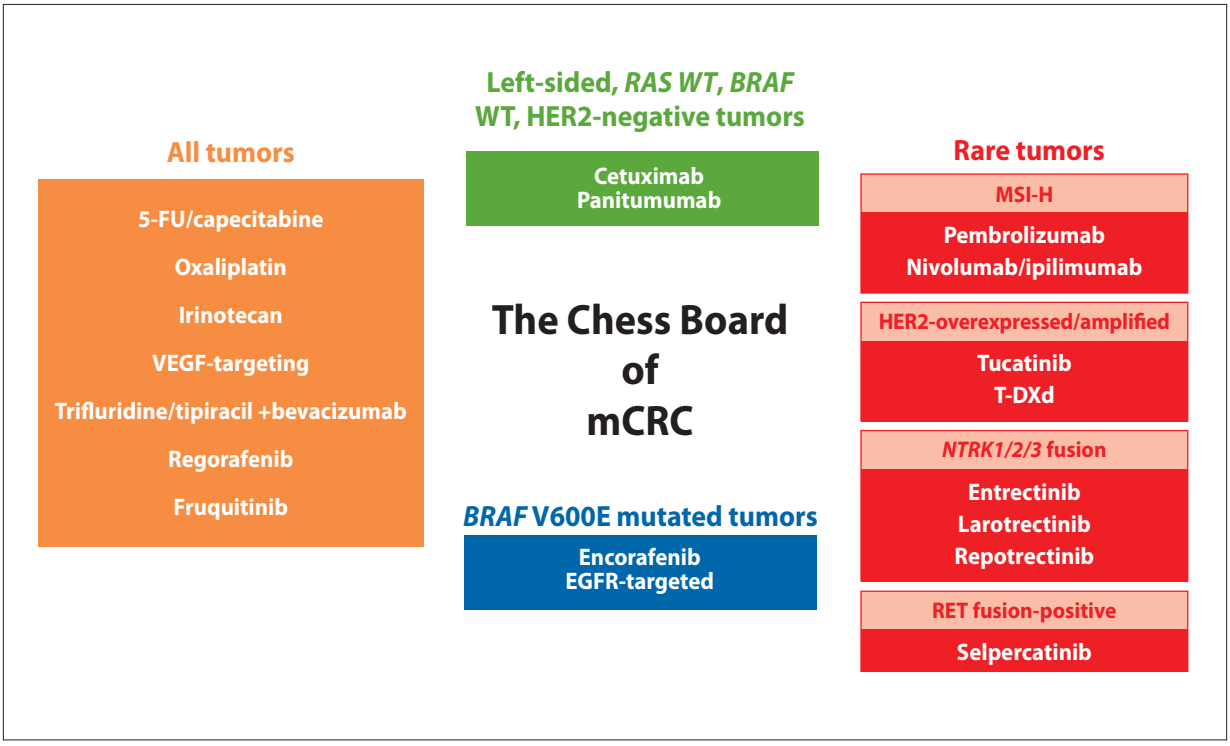

Figure 1. The chess board of mCRC.[4]

5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; T-DXd, trastuzumab deruxtecan; VEGF, vascular endothelial growth factor; WT, wild type.

PET scan was positive for peritoneal lesions and paraaortic nodes. She received leucovorin, 5-FU, and oxaliplatin (FOLFOX), panitumumab, and encorafenib, which induced a near radiographic complete response (CR) but caused a minor rash. The oxaliplatin and fluorouracil were discontinued and the patient continued panitumumab and encorafenib. After 6 months of SD, scans revealed progressive disease but no new symptoms. The patient was started on trifluridine/tipiracil plus bevacizumab and has had SD for 8 months.

The Common Thread: Approaching mCRC Treatment as Chess, Not Checkers

With the availability of varied therapies, including chemotherapeutic agents, targeted agents, and immunotherapy, management of mCRC has evolved to be more strategic, analogous to a game of chess rather than checkers (Figure 1). These cases illustrate that mCRC management requires an individualized approach, taking into account disease-related factors (location, resectability, molecular factors, and the pace of progression), patient-related factors (fitness, preferences, and symptoms), and treatment-related factors (efficacy, toxicity, prior treatments received, and the type of response to prior treatments) at each decision step.

It is important that clinicians understand all the "chess pieces" available and learn to use them strategically for the best outcome across the treatment journey of the patient.

In the Clinic...

National Comprehensive Cancer Network (NCCN)–recommended biomarker testing to be ordered as rapidly as possible after diagnosis[4]:

- *KRAS*, *NRAS*, and *BRAF* V600E mutations
- HER2 (*ERBB2*) overexpression/amplification
- Mismatch repair (MMR) or MSI status, if not already done

Testing should be done as a part of a multigene panel testing to identify rare actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK1/2/3*.

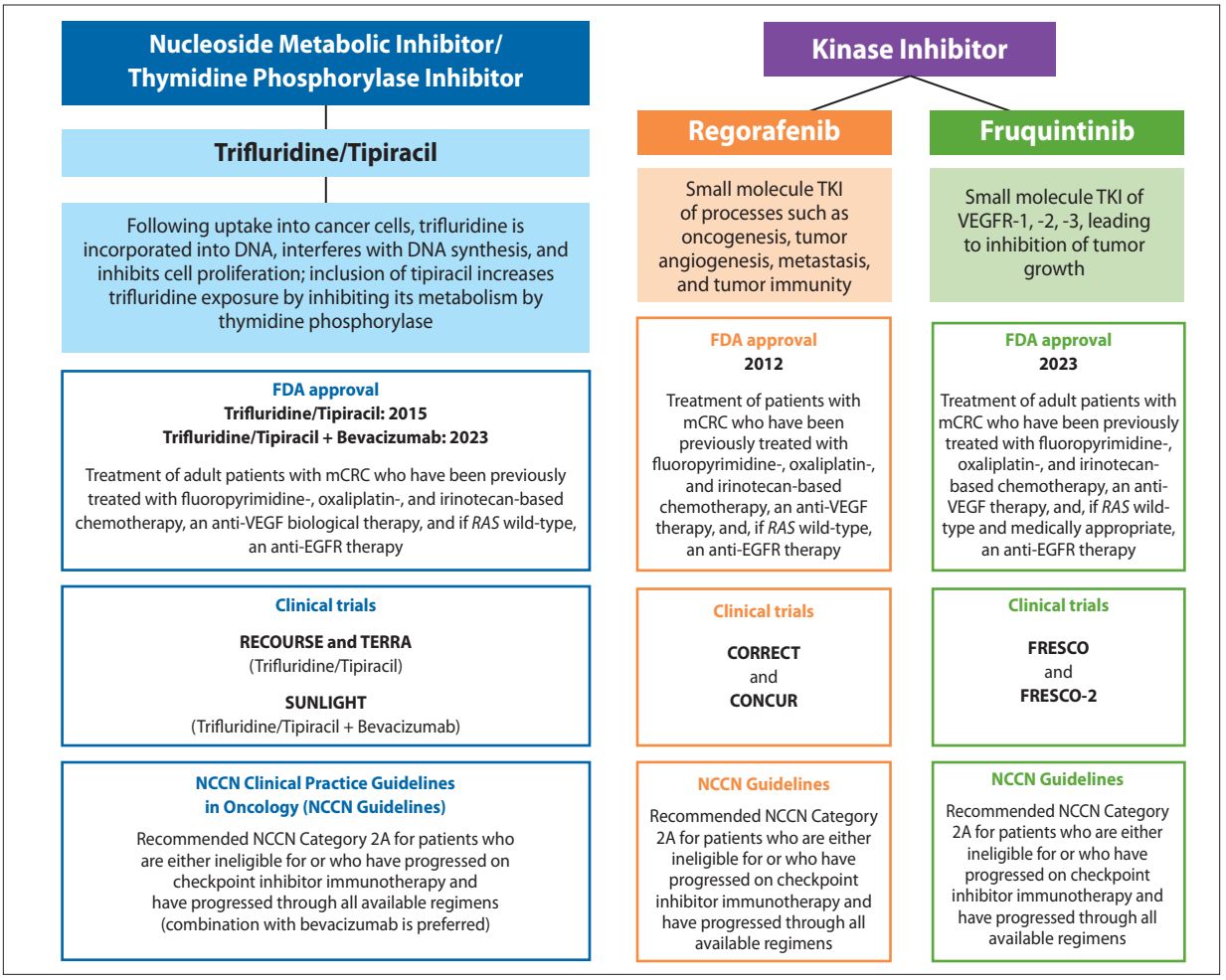

Figure 2. Post–standard therapy agents used in the third line for the treatment of mCRC with no targetable mutations.[4,21-23]

EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; mCRC, metastatic colorectal cancer; NCCN, National Comprehensive Cancer Network; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Overview of mCRC and Initial Assessment

CRC is one of the most common cancer types in the United States; an estimated 158,850 new cases will be diagnosed in 2026, and 55,230 individuals will die from the disease.[1] The age range at diagnosis has shifted, with CRC increasingly affecting younger adults. Although the median age at diagnosis is 66 years, 23.5% of cases occur in adults younger than age 55. Early-onset CRC, defined as occurring in individuals younger than 50 years of age, is among the fastest growing cancers in young people in the United States, with a current incidence rate of 14.8 cases per 100,000 population.[2] There appear to be biological differences among these cancers that may affect the treatment approach, highlighting the importance of molecular testing.

CRC is somewhat unique among cancer types in that some patients with metastatic disease are eligible for curative therapy with surgery or other ablative techniques.[3] As a result, it is essential to conduct a thorough baseline assessment of the location of metastases and to ensure the patient is evaluated by a multidisciplinary tumor board to assess eligibility for potentially curative treatment.

Molecular profiling is another essential element of the workup. Clinicians tend to be familiar with testing for microsatellite instability (MSI), but it is also important to test for other markers, including *BRAF* V600E, HER2 (*ERBB2*), and *KRAS/NRAS*, as the number of actionable alterations increases.[4]

The location of the primary tumor is another key factor; epidermal growth factor receptor (EGFR)-targeted therapy has demonstrated a significant overall survival (OS) benefit in patients with left-sided *RAS* wild-type mCRC.[5]

Table 1. Major Toxicities Associated With Chemotherapies Used in the Treatment of mCRC[6-11]

Chemotherapy	Major toxicities	Clinical impact
5-FU	Diarrhea, mucositis/stomatitis, nausea, myelosuppression, hand-foot syndrome, cardiotoxicity (rare)	May require dose reduction, treatment delay, supportive care, or discontinuation when severe; cardiotoxicity can limit further fluoropyrimidine use
Capecitabine	Hand-foot syndrome, diarrhea, mucositis, fatigue, nausea, myelosuppression	Toxicity can affect adherence and quality of life; dose modification and reduction is a common requirement for hand-foot syndrome and diarrhea
Oxaliplatin	Peripheral sensory neuropathy, myelosuppression, nausea/vomiting, hypersensitivity reactions	Neuropathy is often cumulative and dose-limiting, typically managed with oxaliplatin dose modification; oxaliplatin may be stopped after induction while maintenance therapy continues with 5-FU/leucovorin
Irinotecan	Diarrhea, neutropenia, fatigue, nausea/vomiting, alopecia	Diarrhea and neutropenia can be clinically significant and may require aggressive supportive care, dose reduction, or treatment delay

5-FU, 5-fluorouracil; mCRC, metastatic colorectal cancer.

My Approach to Initial Treatment of mCRC

Initial lines of therapy are determined by tumor location, resectability, and molecular factors. First-line chemotherapy is usually a combination of chemotherapies, typically 5-FU (oral or intravenous) combined with oxaliplatin, irinotecan, or both, usually administered in combination with a biologic agent. It should be noted that these chemotherapy agents are associated with significant hematologic and nonhematologic toxicities (Table 1).[6-11]

For most patients, the added biologic agent is bevacizumab, but EGFR-targeted agents are used in selected patients, and BRAF-targeted drugs are incorporated for patients with a *BRAF* V600E mutation. The treatment approach for patients with deficient mismatch repair (dMMR) and high microsatellite instability (MSI-H) is different and beyond the scope of this article.

When I see a patient with unresectable mCRC, my first question is not simply which regimen to use. It is identifying what the treatment needs to accomplish. I consider multiple factors, including the size of the tumor, types of metastases, and the extent of symptoms. For most patients, I use a 3-drug regimen, typically 5-FU, oxaliplatin, and bevacizumab. However, I may consider a 2-drug regimen of 5-FU and bevacizumab for a patient with small, slow-growing lung metastases, and a 4-drug regimen in a patient with bulky, symptomatic tumors.

The induction regimen is administered for approximately 3 to 6 months, at which point the patient switches to maintenance therapy, typically consisting of a 2-drug regimen of 5-FU and bevacizumab. I tend to use the oral formulation of 5-FU (capecitabine). Usually, this induction strategy helps patients for the first year or more.

Conventional Approaches to Second-Line Therapy: Time to Rethink?

When tumor growth occurs, and the patient is ready for second-line therapy, the reflexive next step has been to administer whichever drugs had not been used in the first-line setting. Typically, this includes irinotecan if not used in induction. The regimen used may vary depending on the presence of targetable alterations such as mutations in *KRAS/NRAS/BRAF* or HER2 overexpression/amplification. Historically, second-line irinotecan-based regimens have yielded only modest efficacy, with objective response rates (ORR) ranging from 4% to 12.5%, increasing to 5% to 24.2% with the addition of a vascular endothelial growth factor (VEGF) inhibitor (bevacizumab, ramucirumab, or aflibercept).[12-16]

The development of disease progression after receiving standard chemotherapy and targeted therapies is considered to be refractory mCRC. Multiple newer agents have demonstrated a significant OS benefit in these patients, including the coformulated chemotherapeutic combination of trifluridine and tipiracil (initially evaluated alone but shown to have a further OS benefit when used in combination with bevacizumab), the VEGF inhibitor fruquitinib, and the multikinase inhibitor regorafenib.[17-20]

Although conventionally patients are considered for these newer approaches only after the standard first-line and second-line regimens, there may be a role for rethinking this paradigm, and considering using these

Table 2. Post–Standard Therapy Agents Used in the Treatment of mCRC With No Targetable Mutations: Summary of Pivotal Trials[17-19,20,24-27]

	Regorafenib		Trifluridine/ Tipiracil		Trifluridine/ Tipiracil + Bevacizumab	Fruquintinib	
Trial	CORRECT	CONCUR	RECOURSE	TERRA	SUNLIGHT	FRESCO	FRESCO-2
Comparator arm	Placebo	Placebo	Placebo	Placebo	Trifluridine/ tipiracil	Placebo	Placebo
Patients, N	760	204	800	406	492	416	691
Median OS, months, HR (95% CI)	6.4 vs 5.0 0.77 (0.64-0.94) *P*=.0052	8.8 vs 6.3 0.55 (0.40-0.77) *P*=.00016	7.1 vs 5.3 0.68 (0.58-0.81) *P*<.001	7.8 vs 7.1 0.79 (0.62-0.99) *P*=.035	10.8 vs 7.5 0.61 (0.49-0.77) *P*<.001	9.3 vs 6.6 0.65 (0.51-0.83) *P*<.001	7.4 vs 4.8 0.66 (0.55-0.80) *P*<.0001
Median PFS, months, HR (95% CI)	1.9 vs 1.7 0.49 (0.42-0.58) *P*<.0001	3.2 vs 1.7 0.31 (0.22-0.44) *P*<.0001	2.0 vs 1.7 0.48 (0.41-0.57) *P*<.001	2.0 vs 1.8 0.43 (0.34-0.54) *P*<.001	5.6 vs 2.4 0.44 (0.36-0.54) *P*<.001	3.7 vs 1.8 0.26 (0.21-0.34) *P*<.001	3.7 vs 1.8 0.32 (0.27-0.39) *P*<.0001
Grade ≥3 AEs in ≥5% in test arm	HFSR (17%), fatigue (10%), diarrhea (8%), hypertension (7%), rash or desquamation (6%)	HFSR (16%), hypertension (11%), increased ALT (7%), increased AST (6%)	Neutropenia (38%), leukopenia (21%), anemia (18%), thrombo-cytopenia (5%)	Neutropenia (33.2%), leukopenia (20.7%), anemia (17.7%), lymphopenia (14.4%)	Neutropenia (43.1%), anemia (6.1%), hypertension (5.7%)	Hypertension (21.2%), HFSR (10.8%)	Hypertension (14%), asthenia (8%), HFS (6%)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

chess pieces earlier in the game. First, let us review the evidence for these newer therapies.

Therapies for Refractory mCRC: A Review of the Evidence

Today the treatment options available for patients with mCRC who have received prior oxaliplatin and irinotecan and are not eligible for targeted therapy include trifluridine/tipiracil with or without bevacizumab (with the bevacizumab combination preferred), fruquitinib, and regorafenib (Figure 2).[21-23] An overview of the clinical trial data leading to the United States Food and Drug Administration (FDA) approval of these regimens is shown in Table 2 (dosing summary in Table 3).[17-19,20,24-27]

Regorafenib

The first drug to receive FDA approval in refractory mCRC was the oral multitargeted tyrosine kinase inhibitor (TKI) regorafenib, which was compared against placebo in the randomized, phase 3 CORRECT trial in 760 patients with mCRC previously treated with standard therapies.[17] The trial was conducted across 16 countries and included 111 Asian patients, primarily Japanese. Patients were randomly assigned 2:1 to best supportive care plus regorafenib 160 mg (n=505) or placebo (n=255) once daily for 3 weeks of every 4-week cycle.

The CORRECT trial met its primary endpoint, demonstrating a significant improvement in OS with regorafenib compared with placebo (median, 6.4 months vs 5.0 months, respectively; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; *P*=.0052). The most common grade 3 or higher adverse events (AEs) related to regorafenib were hand-foot skin reaction (HFSR, 17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash/desquamation (6%).

A second phase 3 trial, CONCUR, evaluated regorafenib in a broader population of Asian patients—204 patients in China, Hong Kong, South Korea, Taiwan, and Vietnam.[24] Patients were randomly assigned 2:1 to regorafenib 160 mg (n=136) or placebo (n=68) once

daily for 3 of 4 weeks with best supportive care. After a median follow-up of 7.4 months, regorafenib was associated with a significant improvement in OS over placebo (median, 8.8 months vs 6.3 months, respectively; HR, 0.55; 95% CI, 0.40-0.77; *P*=.00016). The most frequent treatment-related AEs in the regorafenib arm were HFSR (16%), hypertension (11%), hyperbilirubinemia (7%), hypophosphatemia (7%), increased alanine aminotransferase (7%), increased aspartate aminotransferase (6%), increased lipase (4%), and rash (4%).

Trifluridine/Tipiracil

The second regimen to receive FDA approval in refractory mCRC was trifluridine/tipiracil (TAS-102), an orally administered combination of the thymidine-based nucleic acid analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil. The cytotoxic effects of the compound are exerted by trifluridine, which incorporates into DNA; the addition of tipiracil prevents trifluridine degradation, which stabilizes the active drug.[28]

The randomized, phase 3 RECOURSE trial compared trifluridine/tipiracil against placebo in a global population of patients with refractory mCRC.[25] A total of 800 patients were randomly assigned 2:1 to trifluridine/tipiracil (n=534) or placebo (n=266); patients received trifluridine/tipiracil (35 mg/m^2) or placebo twice daily for 5 days a week with 2 days of rest for 2 weeks, followed by a 14-day rest period, in 4-week cycles. The trial demonstrated a significant improvement in OS with trifluridine/tipiracil vs placebo (median, 7.1 months vs 5.3 months, respectively; HR, 0.68; 95% CI, 0.58-0.81; *P*<.001). The most frequent clinically significant AEs associated with trifluridine/tipiracil were neutropenia (38%), leukopenia (21%), febrile neutropenia (4%), and 1 death. The median time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status from 0 or 1 to 2 or higher was significantly longer with trifluridine/tipiracil vs placebo (5.7 vs 4.0 months; HR, 0.66; 95% CI, 0.56-0.78; *P*<.001).

Trifluridine/tipiracil was also evaluated in the randomized, phase 3 TERRA trial, which focused on an Asian patient population.[26] The trial enrolled 406 patients with mCRC refractory or intolerant to 3 or more prior chemotherapy regimens who were randomly assigned to trifluridine/tipiracil (n=271) or placebo (n=135). Trifluridine/tipiracil was associated with a significant improvement in OS over placebo (median, 7.8 months vs 7.1 months, respectively; HR, 0.79; 95% CI, 0.62-0.99; *P*=.035). The rate of serious AEs was similar between arms (23.2% and 23.7%, respectively).

Trifluridine/Tipiracil + Bevacizumab

The demonstrated benefit of continuing antiangiogenesis therapy after progression, and the demonstration of OS benefit with VEGFR targeting via regorafenib and fruquitinib in refractory mCRC, provided a rationale for evaluating the addition of bevacizumab to trifluridine/tipiracil in this setting.[12,17,19,20,24] Several phase 1/2 trial and investigator-initiated studies demonstrated encouraging efficacy with the addition of bevacizumab to trifluridine/tipiracil, warranting a larger trial.[29-31]

The randomized, phase 3 SUNLIGHT trial was undertaken to evaluate the efficacy and safety of adding bevacizumab to trifluridine/tipiracil in patients with refractory mCRC.[19] The trial enrolled 492 patients who had received up to 2 prior chemotherapy regimens for advanced CRC; patients were randomly assigned 1:1 to trifluridine/tipiracil alone or with bevacizumab administered at 5 mg/kg intravenously on days 1 and 15 every 28 days. The trial met its primary endpoint, demonstrating a significant improvement in OS with trifluridine/tipiracil plus bevacizumab vs trifluridine/tipiracil alone (median, 10.8 vs 7.5 months; HR, 0.61; 95% CI, 0.49-0.77; *P*<.001). The median PFS was 5.6 months and 2.4 months, respectively (HR, 0.44; 95% CI, 0.36-0.54; *P*<.001).

The most common grade 3 or 4 AEs in both arms were neutropenia (43.1% vs 32.1%), neutrophil count reduction (8.9% vs 5.3%), anemia (6.1% vs 11.0%), hypertension (5.7% vs 1.2%), and asthenia (4.1% vs 4.1%). The median time to worsening of ECOG performance status from 0 or 1 to 2 or higher was 9.3 months with trifluridine/tipiracil plus bevacizumab vs 6.3 months with trifluridine/tipiracil alone (HR, 0.54; 95% CI, 0.43-0.67).

The OS benefits observed with trifluridine/tipiracil

In the Clinic...

From "Checkers" to "Chess": Rethinking Treatment Sequencing

Conventionally, mCRC treatment is considered to be sequential with a predetermined first-line, second-line, and third-line algorithm. However, treatment sequencing must be adapted according to disease growth rate, symptoms, prior treatment exposure, molecular characteristics, toxicities, patient lifestyle and preferences, and the need for tumor regression vs disease stabilization. This makes the chess metaphor particularly relevant: some "pieces" are best at producing tumor regression while others aim to stabilize disease. The oncologist needs to decide when to deploy each option.

Table 3. Dosing Summary for Post–Standard Therapy Agents Used in the Treatment of mCRC With No Targetable Mutations[21-23]

Parameter	Regorafenib	Trifluridine/Tipiracil	Fruquitinib
Recommended dosage	160 mg orally once daily for the first 21 days of each 28-day cycle	35 mg/m^2/dose orally twice daily on days 1-5 and 8-12 of each 28-day cycle	5 mg orally once daily for the first 21 days of each 28-day cycle
Dosing considerations	Take after a low-fat meal that contains <600 calories and <30% fat	Take with food	Take with or without food
Dosage forms and strength	Tablet: 40 mg	Tablet: 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil	Capsule: 1 mg and 5 mg
Missed dose	Advise patients to take any missed dose on the same day as soon as they remember; do not take 2 doses on the same day to make up for a missed dose	Advise patients not to retake doses that are vomited or missed and to continue with the next scheduled dose	Advise patients to take a missed dose if less than 12 hours have passed since the missed dose Do not take 2 doses on the same day to make up for a missed dose Do not take an additional dose if vomiting occurs after dose but continue with the next scheduled dose
Dose modifications	Reduce the dose in 40-mg (1 tablet) increments Lowest recommended daily dose: 80 mg	Obtain CBC prior to and on day 15 of each cycle Specific considerations for initiating cycle, holding dose within a cycle, and resuming drug post recovery[a] Maximum of 3 dose reductions permitted Permanently discontinue in patients unable to tolerate 20 mg/m^2 orally twice daily Do not escalate dosage after it has been reduced	First dose reduction: 4 mg orally once daily Second dose reduction: 4 mg orally once daily Permanently discontinue in patients unable to tolerate 3 mg once daily

[a]Do not initiate cycle until: ANC ≥1500/mm^3 or febrile neutropenia resolved; platelets ≥75,000/mm^3; grade 3/4 nonhematologic ARs resolved to grade 0-1. Within a cycle, withhold dose for: ANC <500/mm^3 or febrile neutropenia; platelets <50,000/mm^3; grade 3/4 nonhematologic ARs. Post recovery, resume drug after reducing dose by 5 mg/m^2/dose from the previous dose if the following occur: febrile neutropenia; uncomplicated grade 4 neutropenia (recovered to ≥1500/mm^3) or thrombocytopenia (recovered to ≥75,000/mm^3) that results in >1-week delay in start of next cycle; nonhematologic grade 3 or 4 ARs, except grade 3 nausea and/or vomiting controlled by antiemetic therapy or grade 3 diarrhea responsive to antidiarrhea medication.

ANC, absolute neutrophil count; AR, adverse reaction; CBC, complete blood count; mCRC, metastatic colorectal cancer.

over placebo in the RECOURSE and TERRA trials and with the addition of bevacizumab to trifluridine/tipiracil in the SUNLIGHT trial were sustained across subgroups, including whether patients had *KRAS*-mutated disease.[18,19,25]

Fruquitinib

The oral VEGFR inhibitor fruquitinib was evaluated in patients with refractory mCRC in 2 randomized, phase 3 trials: the FRESCO trial, conducted in China, and the FRESCO-2 trial, which enrolled a broader population.[20,27] In the FRESCO trial, 416 patients in China with mCRC previously treated with at least 2 lines of chemotherapy but not VEGFR inhibitor therapy were randomly assigned to fruquitinib 5 mg (n=278) or placebo (n=138) once daily for 21 days followed by 7 days off in 28-day cycles.[27] Fruquitinib was associated with a significant improvement over placebo in OS (median, 9.3 vs 6.6 months; HR, 0.65; 95% CI, 0.51-0.83; *P*<.001). The rates of serious AEs with fruquitinib and placebo were 15.5% and 5.8%, respectively, and rates of hospitalization were 14.4% and 5.1%, respectively.

The FRESCO-2 trial enrolled patients across 14 countries with mCRC who had received all approved cytotoxic and targeted therapies and progressed on, or were intolerant of, trifluridine/tipiracil, regorafenib, or both.[20] Patients were randomly assigned to fruquitinib 5 mg (n=461) or placebo (n=230) once daily on days 1 to

21 every 28 days with best supportive care. Median OS was significantly longer with fruquitinib compared with placebo (7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; *P*<.0001). Grade 3 or higher AEs occurred in 63% and 50% of patients, respectively. The most frequent grade 3 or higher AEs in the fruquitinib arm were hypertension (14%), asthenia (8%), and hand-foot syndrome (6%). There was 1 treatment-related death reported in each arm: intestinal perforation in the fruquitinib arm and cardiac arrest in the placebo arm.

Strategically Approaching mCRC Across Lines of Therapy

The introduction of newer effective therapies provides options for patients with refractory mCRC. However, simply following the sequential first-line, second-line, and third-line continuum is more of a checkers-type approach. Rethinking this convention and instead using the available agents strategically based on the disease profile, symptoms, and other factors is needed.

Reconsidering Treatment Sequencing

In some cases, an intensive second-line-type regimen is urgently needed for tumor shrinkage. This is akin to using the most powerful chess pieces to counter a strong opponent. However, similar to risks with playing powerful chess pieces, there are downsides with using intensive regimens in terms of tolerability, quality of life (QOL), and potentially losing out on later options. Thus a strategic approach is knowing when to use the most intensive regimens and when instead to use a less-intensive regimen with a primary aim of tumor stabilization and saving the more aggressive regimens when regression is needed. This maximizes the tolerability, QOL, and OS benefits of these regimens, and increases the likelihood of a patient being able to receive all available therapies over the course of their treatment.

Let us consider a patient who develops low-level progressive disease while receiving post-induction maintenance therapy. If the patient is asymptomatic with a good QOL, I will often hold off on irinotecan and other more intensive regimens and instead bring in one of the newer third-line regimens such as trifluridine/tipiracil plus bevacizumab in a second maintenance-type approach.

Locoregional therapy is increasingly being used in the setting of mCRC and highlights the importance of multidisciplinary care. For patients with unresectable colorectal liver metastases, locoregional options that may be considered include hepatic artery infusion pump therapy, stereotactic body radiation therapy, image-guided ablation, and transarterial chemoembolization or radioembolization.[32]

Lack of Evidence for Chemotherapy Rechallenge

Chemotherapy rechallenge is often used in managing mCRC. However, whether oxaliplatin was held in the prior course to avoid neuropathy or whether the patient discontinued oxaliplatin after attaining a response to first-line therapy, oxaliplatin rechallenge is not an evidence-based strategy. Historical data suggest relatively limited response rates and a lack of OS benefit.[33-36] As a result, using rechallenge before third-line therapy is not a good chess move compared with using a later-line therapy with a demonstrated OS benefit.

In the Clinic...

If an effective therapy is saved until too late, the patient may never get the opportunity to receive it. In selected patients, I consider trifluridine/tipiracil plus bevacizumab earlier than its conventional position in the treatment sequence. This is an individualized approach.

Looking Ahead: Clinical Trials and Emerging Strategies

The treatment landscape could change further with the introduction of additional agents. In the STELLAR-303 trial, the investigational multitargeted TKI zanzalintinib plus atezolizumab provided a significant OS improvement over regorafenib in patients with refractory mCRC that is not dMMR/MSI-H, with a median OS of 10.9 vs 9.4 months (HR, 0.80; *P*=.0034).[37]

In May 2026, the Colorectal Cancer Alliance and the Global Coalition for Adaptive Research announced a collaboration to establish an adaptive clinical trial platform called KLEOS that will allow for more rapid and efficient study of new therapies and combinations.[38] I am pleased to be serving as the principal investigator of this initiative, which also plans to assess the potential role of early interventions, including the use of perioperative chemotherapy and treatment upon detection of ctDNA-positive minimal residual disease prior to full disease progression.

Back to the Clinic . . .

To summarize, the management of mCRC continues to evolve, with several newer options that have been evaluated in the third-line setting and beyond. Although the treatment algorithm for mCRC conventionally involves

the sequential use of the most intensive chemotherapy-based regimens at each step, this may not be the optimal approach for each patient, because the goal is not always immediate tumor shrinkage; maintaining disease control, QOL, and access to effective therapies over time can be equally important.

This approach is seen in the 3 cases discussed initially, in which treatment decisions were individualized. In Case 1, less-intensive therapy was shown to preserve QOL and future treatment options in asymptomatic, indolent disease. In Case 2, de-escalation after response preserved QOL, highlighting the use of less-intensive therapies strategically when immediate tumor shrinkage is not required. In Case 3, molecular profile, treatment response, and toxicities determined the treatment strategy.

Furthermore, collaboration with a multidisciplinary team is essential to ensure patients are considered for curative therapy and for potentially beneficial locoregional therapy. Novel therapies and use of innovative clinical trial platforms to evaluate new therapies and combinations will further improve outcomes for patients with mCRC.

For practicing community oncologists faced with a continually evolving treatment landscape, the challenge in mCRC treatment is to move beyond awareness of individual therapies and toward strategic use the available approaches throughout the course of disease.

Disclosures

Dr Marshall has advisory/consulting relationship with Caris, Astellas, Takeda, and Taiho.

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