

Metastatic Colorectal Cancer: Considerations for Treatment in the Third Line and Beyond

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- › A Decade of Progress: Advances in the Third-Line Treatment of Patients With Metastatic Colorectal Cancer
- › Sequencing Considerations in the Third-Line Treatment of Metastatic Colorectal Cancer

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Metastatic Colorectal Cancer: Considerations for Treatment in the Third Line and Beyond

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] provides managed care audiences with an overview of the management of metastatic colorectal cancer in the third-line setting. With an emphasis on therapies used in the absence of targetable biomarkers, it reviews important safety and sequencing considerations for therapies given in the third line.

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A Decade of Progress: Advances in the Third-Line Treatment of Patients With Metastatic Colorectal Cancer

Tanios Bekaii-Saab, MD

Introduction

Colorectal cancer (CRC) is the third most common cancer type in the United States. It accounts for 8% of all new cancer cases for both males and females, with an estimated 153,000 new cases diagnosed in 2023.¹ That year, CRC was the third leading cause of cancer death when stratified by sex, with over 52,000 expected CRC-related deaths reported in men and women combined.¹

The rate of CRC diagnosis remains high; however, both incidence and mortality rates have declined over past decades. For example, the incidence rate was 38.7 per 100,000 people in 2016 as compared with 60.5 per 100,000 people in 1976; this reduction was accompanied by a decrease by more than 50% in peak mortality rates over those 40 years.² These improvements largely can be attributed to improved screening, better treatments, and the identification of biomarkers.² Despite this success, there is a discrepancy among age groups, in which patients 65 years or older have a decreasing incidence rate of 3.3% annually, but patients younger than 50 years have an increasing incidence rate of 2% annually (and a 1.3% annual increase in death rates).²

At the time of CRC diagnosis, as many as 23% of patients have metastatic CRC (mCRC).³ An estimated 25% to 50% of patients diagnosed with lymph node–positive CRC also may develop metastases eventually.⁴ Outcomes for patients with CRC become progressively worse when cancer becomes metastatic, with a 5-year survival rate of 15.6% for patients with mCRC compared with 91% for those with localized disease.³

Economic Impact of mCRC

CRC is the malignancy associated with the second highest costs, accounting for \$24.3 billion in national health care expenditures in 2020 per the National Institutes of Health.⁵ According to Medicare Parts A and B claims for billed services that year, \$23.7 billion was spent on medical services (eg, hospitalizations, outpatient hospital services, infusion and injectable drugs, hospice care, and home health care).⁵ In addition, as estimated using Medicare Part D claims, \$600 million was spent on oral prescription drugs.⁵

Few recent studies have been conducted to evaluate the costs related to mCRC and its management in the United States.

ABSTRACT

The treatment of metastatic colorectal cancer (mCRC) remains challenging. There has been substantial progress in understanding the molecular pathology of the disease that has led to meaningful advancements in treatment options with varying mechanisms of action, although treatment remains costly. Cytotoxic therapies, which are typically combined with targeted therapies, remain the mainstay of first- and second-line treatment for mCRC. While also relevant in earlier lines of therapy, molecular testing has become increasingly important to guide therapy across lines of therapy, for which treatment options are limited. A paucity of data exists in establishing clinical criteria for optimizing the sequencing of therapies in the third line and beyond. A customized approach should consider the efficacy of the therapy balanced with the patient's goals. Sequencing criteria should include a consideration for exposing patients to as many different modes of therapy as possible while preserving quality of life, avoiding serious toxicities, and accounting for the potential impact of cumulative toxicities from prior therapies.

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For author information and disclosures, see end of text.

One systematic review of direct costs related to treating mCRC was conducted in 2022.⁶ While limited by the inclusion of international studies, the review included US-based studies (14 of 29) and converted all costs to 2018 US\$. The estimated cost of treatment for a patient with mCRC broadly ranged from \$12,346 to \$293,461; the wide range was attributable largely to the heterogeneity of treatment. The same study found that estimated average costs for patients receiving systemic therapy could be as high as \$300,000 due to the costs of biologic agents. A major cost driver in the treatment of patients with metastatic disease is the treatment of hematologic adverse events (AEs), such as neutropenia, thrombocytopenia, and/or anemia, associated with cytotoxic treatment.⁷

Review of Molecular Pathology

Roughly 85% of CRCs arise from the alteration in the number and structure of chromosomes known as chromosomal instability. The most clinically relevant pathways for chromosomal instability colorectal tumors are through the Wnt and MAPK pathways. When CRC develops through the Wnt pathway, Wnt proteins bind to a Frizzled family receptor, leading to β -catenin accumulation and hence transcription activation and uncontrolled cell proliferation. In MAPK-activated CRC, receptor tyrosine kinases are activated. Signaling molecules such as RAS and RAF thus become constitutively active, resulting in uncontrolled cell proliferation.⁸

The remaining 15% of CRCs that are not attributed to chromosomal instability arise as a result of microsatellite instability (MSI), a general instability of DNA sequences (known as microsatellites) resulting from either mutation of a mismatch repair (MMR) gene or hypermethylation and subsequent silencing of the *MLH1* promoter.⁸ In the absence of any of the 5 MMR gene mutations of interest (ie, mutation of *MLH1*, *MSH2*, *MSH6*, or *PMS2* or hypermethylation of *MLH1*), the tumor is considered microsatellite stable (MSS). If at least 2 of these MMR genes are mutated, the tumor is considered MSI-high (MSI-H).⁸ This distinction between MSS and MSI-H disease is crucial—it substantially impacts the treatment choice for mCRC.

Molecular Testing

Molecular testing has accelerated the development of biomarker-targeted therapies for CRC, and it may improve outcomes of patients with metastatic disease.⁹ If biomarker testing indicates the presence of identifiable, targetable defects, then therapy can be tailored for that patient.² The **Table** summarizes the range of biomarkers that may be relevant in guiding therapy for patients with mCRC.^{2,10,11} The 2024 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Colon Cancer (version 1.2024) include checkpoint inhibitor therapy options: nivolumab \pm ipilimumab, pembrolizumab, or dostarlimab-gxly. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns.²

Activation of EGFR, a family of receptors including HER2, can trigger a series of downstream signaling pathways leading to cellular proliferation; EGFR is overexpressed in as many as 77% of patients with CRC.⁹ The oncogenes *KRAS* and *BRAF* are major contributors to the chromosome instability found in 85% of CRC cases and are associated with resistance to anti-EGFR therapy.^{2,9}

For patients with mCRC, the 2024 NCCN Guidelines in Oncology Colon Cancer (version 1.2024) and Rectal Cancer (version 1.2024) currently recommend broad molecular profiling; this should include testing for common biomarkers (eg, mutations in *KRAS/NRAS* and *BRAF*, amplification of *HER2*, and MSI) and rare biomarkers (eg, mutations in *POLE/POLD1*, *RET*, and *NTRK*).^{2,12}

Current Treatment Landscape for mCRC in the First and Second Line

Current treatment pathways for patients with unresectable mCRC involve multiple lines of therapy—and these pathways have changed dramatically over the past few decades with the advent of biologic agents and immunotherapy. First-line (1L) treatment typically involves a combination of 1 or more chemotherapeutic agents (eg, FOLFOX [leucovorin, fluorouracil, and oxaliplatin], or FOLFIRI [leucovorin, fluorouracil, and irinotecan]) with or without a monoclonal antibody.² In the absence of targetable mutations, this is followed by second-line (2L) treatment with a different chemotherapeutic regimen (typically, the alternative 1L option that was not given initially) with or without a monoclonal antibody.²

Anti-VEGF Therapy

VEGF (in particular, VEGF-A) expression is increased in CRC, and this increase plays an important role in promoting tumor angiogenesis and, subsequently, tumor growth and metastases.¹³ Bevacizumab, a VEGF-A inhibitor, was approved in 2004 for the treatment of mCRC; it prevents the interaction of VEGF with its receptors, reduces microvascular growth, and inhibits metastatic disease progression.¹⁴ The addition of bevacizumab to chemotherapy has shown benefit in both progression-free survival (PFS) and overall survival (OS) across multiple lines of therapy.¹⁵⁻¹⁷

Anti-EGFR Therapy

Treatments for mCRC can involve targeting the EGFR pathway through use of anti-EGFR monoclonal antibodies. Cetuximab, approved by the FDA in 2004, binds to the external domain of EGFR and promotes internalization and degradation of the receptor.^{9,18} Panitumumab, another EGFR inhibitor indicated for treatment of mCRC, was approved in 2006.¹⁹ By binding specifically to EGFR and competitively inhibiting the binding of other ligands, panitumumab prevents ligand-induced receptor autophosphorylation and activation of receptor-associated kinases. However, anti-EGFR therapies are not recommended for patients with tumors with RAS

or *BRAF* mutations downstream signaling pathways, which causes resistance to them.^{9,20} Additionally, the presence of HER2 amplification or right-sided tumor location appear to predict for resistance to anti-EGFR therapies.^{21,22}

Immunotherapy for dMMR/MSI-H or *POLE/POLD1* mutation

In 2020, pembrolizumab, a PD-1 targeting humanized immunoglobulin G4 (IgG4) antibody, was FDA-approved for the treatment of patients with MMR deficiency (dMMR)/MSI-H CRC. Pembrolizumab binds to PD-1 and prevents its interaction with PD-L1 and PD-L2. By doing so, it releases PD-1 pathway-mediated inhibition of immune response, including the antitumor immune response.²³ Additional

NCCN Guidelines preferred PD-1 blockers for dMMR/MSI-H mCRC include nivolumab and dostarlimab.² Additionally, nivolumab can also be used in combination with ipilimumab in either the 1L or later lines of therapy as recommended by the NCCN Guidelines.^{2,24}

Third-Line Treatment Options

Improvements in the efficacy of therapies and the number of lines of therapies available are among possible factors that have improved treatment outcomes for mCRC.²⁵ A growing number of patients with mCRC who receive 1L and 2L chemotherapy are treated with third-line (3L) or subsequent lines of therapy (3L+). This trend highlights the importance of optimizing the selection and sequencing of later-line treatments for these patients.²⁶

TABLE. Key Biomarkers Relevant for Selection of Therapy to Treat mCRC^{2,10,11}

Biomarker	Frequency	Drug selection
<i>KRAS/NRAS</i> mutations	<i>KRAS</i> : 50% • <i>KRAS</i> G12C mutation: 17% of <i>KRAS</i> -mutated mCRC <i>NRAS</i> : 4%	Mutations are associated with resistance to anti-EGFR therapy; do not treat with cetuximab or panitumumab. For <i>KRAS</i> G12C mutations, additional targeted therapy may allow for the use of anti-EGFR therapy. Therapeutic options include: • sotorasib + (cetuximab or panitumumab) • adagrasib + (cetuximab or panitumumab)
<i>BRAF</i> V600E mutations	5%-9%	Mutations are associated with resistance to anti-EGFR therapy; anti-EGFR therapy must be given in combination with a <i>BRAF</i> V600E inhibitor. Targeted therapeutic options include: • encorafenib + (cetuximab or panitumumab)
<i>HER2</i> amplification/overexpression	3%	Treatment with anti-HER2 therapy is recommended in subsequent lines. Targeted therapeutic options (if also <i>RAS/BRAF</i> wild-type) include: • trastuzumab + pertuzumab • trastuzumab + lapatinib • trastuzumab + tucatinib Targeted therapeutic options (regardless of <i>RAS/BRAF</i> status) include: • fam-trastuzumab deruxtecan ^a
dMMR/MSI-H or <i>POLE/POLD1</i> mutation	4%-7%	Treatment with checkpoint inhibitors is recommended. Therapeutic options include ^b : • nivolumab ± ipilimumab • pembrolizumab • dostarlimab
<i>NTRK</i> fusions	0.2%-1%	Targeted therapeutic options include: • entrectinib • larotrectinib
<i>RET</i> fusions	< 1%	Targeted therapeutic options include: • selpercatinib

dMMR, deficient mismatch repair; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; WT, wild-type.

^aHas shown activity in patients who previously received HER2-directed therapy with an objective response rate of 43.8% (95% CI, 19.8-70.1).

^bCheckpoint inhibitor therapy options include: nivolumab + ipilimumab, pembrolizumab, or dostarlimab-gxly. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns.

Best practices for treating patients with mCRC in the 3L are typically made based on considerations of clinical guidelines, patient-specific characteristics (eg, performance status, medical history), disease-specific characteristics (eg, molecular biomarkers, previous therapies received), effective AE management, and patient quality of life (QOL).²⁶⁻²⁸

Given the complexity and patient-specific nature of these treatment decisions, clinical pathways should allow for flexibility for any FDA-approved therapy in the 3L setting and beyond.

Patients who experience relapse of disease after prior lines of treatment have a limited number of alternatives. One is treatment with cetuximab or panitumumab for any patient who has not previously received these drugs; this, however, is a less common 3L treatment, as these are typically administered in an earlier line of therapy. If the mCRC is dMMR/MSI-H or harbors the *POLE/POLD1* mutation, immunotherapy can still be considered if it was not received in a previous line; however, similar to anti-EGFR therapies, immunotherapies are often used earlier in a patient's treatment course.² Another option is to leverage biomarker-targeting therapies (eg, agents targeting HER2, *BRAF* V600E, *NTRK*, and *RET* [Table]).^{2,27}

In addition, patients with mCRC in the 3L have access to several therapies in different classes that are indicated specifically for the 3L and beyond. These include yet another chemotherapeutic agent (ie, trifluridine/tipiracil [FTD/TPI], given alone or with bevacizumab) or an agent other than a chemotherapeutic drug (eg, regorafenib, fruquintinib).² Recognition that repeated use of chemotherapies can be associated with substantial AEs, such as myelosuppression, has fueled interest in treatment regimens used in the 3L that offer improved safety and tolerability.²⁹

Regorafenib

Regorafenib, an oral multikinase inhibitor approved by the FDA in 2012, remains a core standard of care option for patients who have been previously treated for mCRC. In addition to its other indications in hepatocellular carcinoma and metastatic gastrointestinal stromal tumor, regorafenib is indicated to treat patients with mCRC who have been previously treated with chemotherapy (including a fluoropyrimidine, oxaliplatin, and irinotecan) and biologic therapies (ie, an EGFR inhibitor [if *RAS* wild-type] or a VEGF inhibitor).³⁰ Regorafenib has a unique mechanism of action; it inhibits at least 20 membrane-bound and intracellular kinases involved in oncogenesis, tumor angiogenesis, metastasis, and tumor immunity. Kinases involved are RET, RAF, BRAF, and VEGFR, among others.³⁰

The efficacy of regorafenib was demonstrated in the multicenter, randomized, double-blind, placebo-controlled CORRECT trial (NCT01103323) that evaluated OS, PFS, objective tumor response rate, and disease control rate in 760 patients with previously treated mCRC.³¹ In this trial, patients were randomly assigned 2:1 to receive

160 mg once daily of regorafenib plus best supportive care (BSC) (505 patients) or placebo plus BSC (255 patients) on days 1 through 21 of a 28-day cycle.

Patients receiving regorafenib plus BSC demonstrated statistically significant improvements in both OS and PFS when compared with patients receiving placebo plus BSC. Patients experienced OS that was 1.4 months longer than noted in those given placebo (HR, 0.77; 95% CI, 0.64-0.94; $P = .0052$) and PFS that was 0.2 months longer than seen in those given placebo (HR, 0.49; 95% CI, 0.42-0.58; $P < .0001$).³¹ Results of a phase 3 trial of 204 patients at study sites throughout China, Hong Kong, South Korea, Taiwan, and Vietnam showed similar results.³²

The rate of AEs in the CORRECT trial was high, with 93% of patients experiencing an AE of any grade in the regorafenib arm.³¹ The most common any-grade AEs included fatigue (47%), hand-foot skin reaction (HFSR) (47%), diarrhea (34%), and anorexia (30%). HFSR and fatigue of at least grade 3 were observed in 17% and 10% of patients, respectively. Notably, incidence of myelosuppression of grade 3 or more was low with regorafenib (grade 4, $\leq 5\%$; grade 4, $\leq 1\%$).³⁰ Dose reduction or interruption was needed for 67% of patients receiving regorafenib vs 23% of those given placebo.³¹ AEs resulting in discontinuation occurred in 8.2% of patients receiving regorafenib compared with 1.2% of those receiving placebo, with HFSR and rash being the most common reasons for permanent discontinuation of regorafenib.³⁰

Based on the rate of AEs in the CORRECT trial, the multicenter, phase 2, open-label ReDOS trial (NCT02368886) was initiated in 39 outpatient cancer centers in the United States to explore dose optimization strategies for regorafenib.³³ Enrollment in this study occurred between June 2, 2015, and June 22, 2017; patients were randomly assigned to receive 80 mg once daily of regorafenib orally with weekly dose-escalation or a steady dose of 160 mg once daily. In both groups, regorafenib was administered for 21 consecutive days of a 28-day cycle. During subsequent cycles, patients received the highest tolerated dose from cycle 1, up to 160 mg. The primary end point of this study was the percentage of patients able to complete 2 full cycles of treatment and begin the third cycle. Secondary end points included efficacy end points such as PFS, OS, time to progression, as well as cumulative dose received within the first 2 cycles, proportion of patients with HFSR of at least grade 3, and QOL measures.

The dose-escalation strategy resulted in 43% of patients (95% CI, 29%-56%) successfully initiating treatment cycle 3 as compared with 26% of patients (95% CI, 15%-37%) starting with full-dose therapy; the difference was significant ($P = .043$).³³ The main factor preventing patients from starting a third cycle was progression of disease (dose-escalation group, 37%; standard-dose group, 47%). There was a 3.8-month difference in OS between the dose-escalation group and the standard-dose group (9.8 vs 6.0 months; HR, 0.72;

95% CI, 0.47-1.10; log-rank $P = .12$). Additionally, the incidence of grade 3 AEs commonly associated with regorafenib treatment—specifically fatigue, HFSR, and hypertension—were numerically lower in the dose-escalation group than in the standard-dose group. This numerical reduction in the incidence of fatigue, HFSR, and hypertension was further supported by the results of another phase 2 study that evaluated a slightly modified dose-escalation strategy that started at 120 mg daily.³⁴ Overall, these data suggest that more patients are able to tolerate regorafenib with a dose-escalation strategy of regorafenib.

Based on results from these trials, the NCCN Guidelines recommend use of regorafenib for patients with mCRC who are refractory to chemotherapy; it is to be given before or after FTD/TPI, FTD/TPI plus bevacizumab, or fruquintinib. They also recommend use of the dose-escalation strategy tested in the ReDOS trial as an appropriate alternative dosing approach.² Patients receiving regorafenib may experience AEs such as fatigue, HFSR, and hypertension; still, this medication may be an option in patients for whom a chemotherapy-sparing option is needed and AEs such as myelosuppression must be avoided.

Trifluridine/tipiracil

FTD/TPI, an oral chemotherapeutic agent, was approved by the FDA in 2015 for the treatment of adults with mCRC who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biologic therapy; and, if RAS wild-type, an anti-EGFR therapy.³⁵ FTD/TPI consists of 2 agents: trifluridine (a thymidine-based nucleoside analog) and tipiracil (a thymidine phosphorylase inhibitor that helps prevent the breakdown of active trifluridine). Trifluridine is incorporated into the DNA of cancer cells, disrupting the process of DNA synthesis and hindering cellular growth.³⁵

In the RECURSE clinical trial (NCT01607957), investigators evaluated FTD/TPI monotherapy.³⁶ In this randomized, double-blind, placebo-controlled trial, 534 patients with mCRC who were previously treated with at least 2 lines of chemotherapy were randomly assigned to receive FTD/TPI plus BSC, and 266 participants were given placebo plus BSC. FTD/TPI was taken orally twice daily on days 1 to 5 and 8 to 12 of a 28-day treatment cycle. The primary end point evaluated was OS, and PFS was a secondary end point.

Treatment with FTD/TPI demonstrated statistically significant improvements in both OS and PFS as compared with placebo. The median OS among patients receiving FTD/TPI was 7.1 months compared with 5.3 months for those receiving placebo (HR, 0.68; 95% CI, 0.58-0.81; $P < .001$).³⁶ Among patients treated in the United States, median PFS was 2.0 vs 1.7 months, respectively (HR, 0.48; 95% CI, 0.41-0.57; $P < .001$).

In the RECURSE trial, 53% of patients treated with FTD/TPI required a delay of at least 4 days before beginning the next cycle

of treatment due to toxicity, 14% of patients required a dose reduction, and 4% of patients discontinued treatment due to AEs.³⁶ AEs of at least grade 3 were observed in 69% of patients treated with FTD/TPI; neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea were the most common AEs or laboratory anomalies leading to dose reduction.

Trifluridine/tipiracil With Bevacizumab

Subsequent to the RECURSE trial, FTD/TPI was evaluated as combination therapy with bevacizumab in the SUNLIGHT trial (NCT04737187); results of this study ultimately led to FDA approval of this combination in August 2023.³⁵ This international, randomized, active-controlled, open-label study involved patients previously treated with mCRC and required that patients have no more than 2 prior treatments for mCRC.¹⁷ In all, 246 patients were randomly assigned to receive FTD/TPI plus bevacizumab, and 246 patients were given FTD/TPI alone. FTD/TPI was administered by mouth twice daily on days 1 to 5 and 8 to 12 of a 28-day treatment cycle, with bevacizumab administered intravenously on days 1 and 15 of each 4-week treatment cycle. The primary treatment end point evaluated was OS, with PFS being a secondary outcome measure.

FTD/TPI plus bevacizumab proved to be statistically superior to FTD/TPI monotherapy for both OS and PFS.¹⁷ Patients receiving FTD/TPI plus bevacizumab demonstrated a median OS of 10.8 months compared with 7.5 months for those receiving FTD/TPI alone (HR, 0.61; 95% CI, 0.49-0.77; $P < .001$). The median PFS was 5.6 vs 2.4 months, respectively (HR, 0.44; 95% CI, 0.36-0.54; $P < .001$). Notably, survival benefits were significantly better with combination treatment regardless of whether patients received previous bevacizumab therapy. However, while patients benefited from treatment with FTD/TPI plus bevacizumab regardless of prior bevacizumab exposure, the benefit was meaningfully larger in patients who had not been exposed to prior bevacizumab. In a subgroup analysis, the median PFS was 7.7 months (95% CI, 6.2-9.4 months) in patients who did not receive prior bevacizumab but 4.5 months (95% CI, 4.1-5.5 months) in those given prior bevacizumab; the median OS was 15.1 months with prior bevacizumab (95% CI, 12.1 months to not evaluable) but 9.0 months without (95% CI, 8.3-10.8 months); however, neither improvement was statistically significant.³⁷

Severe AEs (grade ≥ 3) were reported in 72.4% of patients in the FTD/TPI plus bevacizumab group and 69.5% of the FTD/TPI monotherapy group.¹⁷ The most common AEs (any grade) in both groups were neutropenia, nausea, and anemia. Both the combination and monotherapy groups experienced hematologic toxicity of at least grade 3; specifically, neutropenia (43.1% and 32.1%, respectively), anemia (6.1% and 11.0%, respectively), and thrombocytopenia (2.8% and 1.2%, respectively) were noted. Granulocyte colony stimulating factors were given to 29.3% and 19.5% of patients in the FTD/TPI

plus bevacizumab group and FTD/TPI monotherapy group, respectively.¹⁷ Dose delays were common, occurring in 69.5% of patients using combination therapy and 53.3% of those given monotherapy; AE-related treatment discontinuation occurred in 12.6% of patients in both groups.

FTD/TPI alone or with bevacizumab is recommended by the NCCN Guidelines as an option for patients experiencing disease progression despite standard treatments. The NCCN Guidelines offer no specific guidance or recommendation about sequencing therapy between FTD/TPI, regorafenib, or fruquintinib for patients in the 3L+ setting; however, it does recommend use of FTD/TPI plus bevacizumab over FTD/TPI monotherapy.² FTD/TPI given alone or with bevacizumab may be an option for patients needing to avoid toxicities such as HFSR, but its use may be challenging for those who are unable to tolerate myelosuppression.

Fruquintinib

Fruquintinib, an oral kinase inhibitor approved by the FDA in October 2023, is indicated for patients with mCRC who were previously treated with chemotherapy and biologic agents, having received all of the following: fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and an anti-EGFR therapy if medically appropriate.³⁸ Fruquintinib is a highly selective, small-molecule VEGF inhibitor that selectively inhibits VEGFR1, -2, and -3 to slow tumor growth while having a weak to no inhibitory effect on other kinases.³⁹

Efficacy of fruquintinib was evaluated in the FRESKO-2 trial (NCT04322539), an international, multicenter, randomized, double-blind, placebo-controlled study that randomly assigned 691 patients with mCRC who had disease progression in a 2:1 ratio; 461 patients received fruquintinib orally once daily for the first 21 days of a 28-day cycle plus BSC, and 230 patients received placebo plus BSC.⁴⁰ Notably, a majority of patients (73%) had more than 3 lines of previous therapy (median, 4 previous lines of therapy). Additionally, all patients had previously received regorafenib, FTD/TPI, or both agents. Efficacy was evaluated using the primary end point of OS and the secondary end point of PFS.

Adding fruquintinib to BSC resulted in a median OS of 7.4 months compared with 4.8 months with use of placebo plus BSC (HR, 0.66; 95% CI, 0.55-0.80; $P < .001$).⁴⁰ Fruquintinib plus BSC also demonstrated significant improvements in PFS (3.7 vs 1.8 months, respectively; HR, 0.32; 95% CI, 0.27-0.39; $P < .001$).

Grade 3 or worse AEs occurred in 63% of patients in the fruquintinib group, the most frequent being hypertension (14%), asthenia (8%), and HFSR (6%).⁴⁰ One treatment-related death due to intestinal perforation was reported in the fruquintinib group. AEs in patients receiving fruquintinib resulted in 20% of patients discontinuing treatment, 47% experiencing dose interruptions, and 24% having dose reductions. Among 110 patients, the need to

reduce the dose was most frequently attributed to HFSR (24 patients), hypertension (17 patients), and asthenia (16 patients).⁴⁰ Of note, no hematologic toxicity was observed with fruquintinib.

The NCCN Guidelines include fruquintinib as a recommended therapy for patients with previously treated mCRC who experienced progression with use of all available regimens.² Similar to those given regorafenib, patients receiving fruquintinib may experience AEs such as fatigue, HFSR, and hypertension. However, fruquintinib therapy is another option when chemotherapy (and subsequent myelosuppression) is being avoided.

Sequencing Considerations in the Third Line and Later

To date, no head-to-head or sequencing studies have been conducted to compare these therapies.⁴¹ NCCN Guidelines recognize and recommend regorafenib, FTD/TPI, FTD/TPI plus bevacizumab, and fruquintinib for later-line treatment in patients with refractory disease; however, they acknowledge that no data inform the best order of those therapies, and they state that any of the therapies may be given before or after the others with preference for FTD/TPI plus bevacizumab over FTD/TPI monotherapy.² The complexity of this decision highlights the importance of ensuring availability of all 4 therapies to patients with mCRC so that optimal treatment decisions can be made on a patient-specific basis.

Treating with regorafenib prior to FTD/TPI in the 3L may be preferred due to several factors.⁴² First, many patients reaching 3L treatment may have experienced hematologic AEs from exposure to multiple lines of chemotherapy. A chemotherapy-free interval (ie an interval in which alternative therapies such as targeted therapies or immunotherapy are used) may prove beneficial for select patients whose bone marrow reserves are depleted with use of previous chemotherapy regimens. Additionally, chemotherapy given after regorafenib appears to maintain clinical benefit, and regorafenib may offer a different mechanism of action at this stage of the disease.⁴² Similar to regorafenib, fruquintinib offers a mechanism of action that differs from more conventional chemotherapy to use in the 3L setting and would offer a chemotherapy-free interval with low risk of hematologic toxicity.³⁸

Unmet Needs in Third-Line Treatments

Treatment of patients with cytotoxic therapies in earlier lines can result in hematologic AEs, including anemia and neutropenia. Patients who experience myelosuppression during earlier cycles of chemotherapy may be at increased risk for neutropenic complications in subsequent cycles.⁴³ Long-term use of chemotherapy is often associated with myelosuppression and other hematologic AEs, highlighting the unmet need for other therapeutic strategies.²⁹ Prolonging life while maintaining patient QOL are key treatment objectives for patients with advanced mCRC.⁴⁴ With the overarching

strategy of preserving QOL to the highest degree possible, it's important that patients be exposed to all viable therapeutic options.⁴⁴

Additional studies are needed to determine optimal sequencing of therapies in the 3L and beyond with options such as FTD/TPI alone or with bevacizumab, regorafenib, and fruquintinib to best navigate potential toxicities, preserve patient QOL, and improve OS. More research in the area of relevant and targetable biomarkers is needed in this space to further advance our precision medicine approaches in mCRC.

Conclusion

There has been substantial progress in the treatment of mCRC with ongoing research about the role of predictive biomarkers, creating a complex and evolving clinical landscape. Most patients with mCRC who become refractory to initial lines of chemotherapy become eligible for additional lines of treatment with the goal of controlling disease and preserving an acceptable QOL. Importantly, as the number of lines of treatment increases, the likelihood of treatment-limiting toxicities may also increase. Therapies such as regorafenib, FTD/TPI alone or with bevacizumab, and fruquintinib are recommended by the NCCN Guidelines for use in this setting with treatment decisions relying heavily on patient-specific characteristics. Clinical pathways should retain flexibility to allow therapeutic selection based on patient-specific situations. Details about prior therapy, a patient's individual experience of treatment-related toxicities, and a nuanced understanding of a patient's tumor characteristics should all be weighed carefully when selecting treatment for mCRC in the 3L and beyond. ■

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Sequencing Considerations in the Third-Line Treatment of Metastatic Colorectal Cancer

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Introduction

Colorectal cancer (CRC) remains a substantial global health concern, and the management of metastatic CRC (mCRC) continues to pose clinical challenges to providers and health systems. The primary goals of treatment for patients with metastatic disease are to prolong survival while preserving quality of life (QOL).^{1,2}

Identification of relevant, targetable biomarkers has led to improved outcomes for patients with mCRC.³ However, most patients with mCRC eventually experience disease progression, and they may require subsequent lines of treatment.⁴ Among unmet needs is the objective determination of optimal sequencing in the third or later lines (3L+) of therapy.⁵

As patients progress to later lines of therapies, treatment selection may be guided by prior therapy, toxicity, tumor molecular profile, patient age, performance status, comorbidities, and other factors.^{5,6} Furthermore, with the goal of improving survival while maintaining QOL in mind, sequencing of all treatment options should be optimized to balance risk to benefit ratio.^{2,4}

This article explores sequencing considerations in the 3L treatment of mCRC, emphasizing the importance of tailoring therapeutic approaches to individual patients in an attempt to optimize both survival outcomes and QOL.

Therapy Sequencing of Approved Third-Line Agents

As outcomes for patients with mCRC have improved over past decades, more patients have become eligible for treatment in the 3L+.⁷ Thus, the ability to sequence these therapies in the most effective manner becomes important.

First-line (1L) and second-line (2L) therapies encompass regimens that combine chemotherapy with targeted biologics.⁵ For patients harboring microsatellite instability–high or mismatch repair–deficient tumors, or for those with *POLE* or *POLD1* mutations, use of FDA-approved immunotherapies (eg, pembrolizumab, nivolumab with or without ipilimumab, and dostarlimab) may be considered if immunotherapy was not used during previous lines of therapy. The 2024 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer (version 1.2024) include checkpoint

ABSTRACT

Numerous advances in the standard of care for metastatic colorectal cancer (mCRC), including the approval of several new treatments indicated for treatment in the third line or later (3L+), have been made, yet data and appropriate guidance on the optimal sequencing and treatment strategies for these lines of therapy are lacking. Four treatments—regorafenib, trifluridine/tipiracil alone or with bevacizumab, and fruquintinib—are FDA-approved and recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the treatment of mCRC in the 3L+. When considering sequencing of treatment options for patients in the 3L+, the goal of treatment is to improve survival, but also maintain quality of life, a goal that requires consideration of relative efficacy and cumulative toxicity such as persistent myelosuppression.

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inhibitor therapy options: nivolumab ± ipilimumab, pembrolizumab, or dostarlimab-gxly. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns.^{5,8} In the 3L, there is limited evidence to rechallenge with previously used chemotherapy (eg, oxaliplatin, irinotecan) with data primarily available from single-arm studies with small sample sizes.⁹ Alternatively, providers may introduce new options—notably, regorafenib, trifluridine/tipiracil (FTD/TPI) alone or with bevacizumab, or fruquintinib.^{5,8,10} Multiple 3L+ therapies are approved by the FDA, yet optimal sequencing of these agents remains challenging.⁵

Regorafenib was approved by the FDA in 2012 for the treatment of previously treated mCRC following chemotherapy-based treatments that include a fluoropyrimidine, oxaliplatin, irinotecan, and biologic therapies including anti-VEGF or anti-EGFR therapy, as indicated. It is a small-molecule, multikinase inhibitor that targets at least 20 kinases involved in tumor activity (eg, RET, RAF1, BRAF, and VEGFR).¹¹

Regorafenib therapy was associated with low rates of grade 3 and 4 hematologic adverse events (AEs) in clinical trials.¹¹ In the ReDOS trial, the dose escalation strategy was associated with a lower rate of nonhematologic toxicities of grade 3 or higher when compared with the standard dose, with toxicities still notable as early as cycle 1 (hand-foot skin reaction [HFSR], 7.4%; fatigue, 5.6%; hypertension, 3.7%).¹² Additionally, regorafenib was discontinued in 20% of patients receiving the dose-escalation strategy due to AEs. Patients given regorafenib who had progression-free survival (PFS) for longer than 4 months were more likely to have had an ECOG performance status of 0, a longer time since diagnosis of metastatic disease, and no liver metastases.¹³ NCCN Guidelines[®] and the European Society for Medical Oncology (ESMO) recommend a treatment sequence that may include regorafenib in the 3L setting. This recommendation involves regorafenib use following the completion of 2 prior lines of standard chemotherapy-based regimens.^{8,14}

FTD/TPI is approved for use alone or in combination with bevacizumab in adult patients with mCRC who were previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biologic therapy; and, if RAS wild-type, an anti-EGFR therapy. It consists of trifluridine (a thymidine-based nucleoside analog) and tipiracil (a thymidine phosphorylase inhibitor). FTD/TPI becomes incorporated into cancer cell DNA and subsequently inhibits cellular proliferation.¹⁵

In the pivotal RECURSE trial (NCT01607957), hematologic AEs including neutropenia, anemia, and febrile neutropenia (FN) were among the most common AEs leading to dose reduction.¹⁵ Additionally, 3.6% of patients discontinued FTD/TPI due to AEs. In the SUNLIGHT pivotal trial (NCT04737187), use of FTD/TPI plus bevacizumab produced significant improvement in both PFS and overall survival (OS) over FTD/TPI monotherapy.¹⁶ Notably, this

significant improvement was seen regardless of prior bevacizumab use, although PFS and OS were numerically longer in those who did not receive bevacizumab in prior lines of therapy than in those who did.¹⁶

This draws attention to the possible need to consider a patient's prior use of bevacizumab when deciding whether to use FTD/TPI plus bevacizumab in the 3L. Additionally, neutropenia and anemia were the most common laboratory anomalies or AEs observed among patients treated with either FTD/TPI monotherapy or FTD/TPI plus bevacizumab in this trial.¹⁵ The myelosuppression noted in results of both the RECURSE and SUNLIGHT trials highlights the importance of regularly monitoring patients for hematologic toxicities and adjusting treatment through dose reductions and treatment delays when these toxicities occur.¹⁵ Both the NCCN Guidelines[®] and ESMO recommend both FTD/TPI and FTD/TPI plus bevacizumab as treatment options for those who have progressed through standard therapies; however, they suggest a preference for FTD/TPI plus bevacizumab combination therapy over monotherapy.^{8,17}

Fruquintinib was approved in the US in November 2023 for patients with mCRC who were previously treated with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and, if RAS wild-type and it is medically appropriate, an anti-EGFR therapy.¹⁰ This small-molecule VEGFR inhibitor slows tumor growth by inhibiting VEGF-induced phosphorylation. Patients given fruquintinib in the FRESCO-2 clinical trial (NCT04322539) did not experience higher rates of hematologic AEs when compared with those given placebo, although AEs causing treatment discontinuation were noted in 20% of trial participants given fruquintinib. This drug has been added to the NCCN Guidelines recommendations for the treatment of 3L+ mCRC.⁸

The NCCN Guidelines offer no specific guidance regarding ideal sequencing between these recommended therapeutics.⁸ The decision about how to best sequence patients in 3L+ therapy with regorafenib, FTD/TPI monotherapy, FTD/TPI plus bevacizumab, or fruquintinib requires a case-by-case evaluation.^{8,18}

A US-based retrospective cohort study compared sequential treatment with regorafenib followed by FTD/TPI with or without bevacizumab (R-T) in 393 patients, compared with FTD/TPI with or without bevacizumab followed by regorafenib (T-R) in 435 patients.¹⁹ Median OS was numerically longer for R-T than for T-R, but this finding was not statistically significant (OS, 13.1 vs 11.5 months, respectively; HR, 0.94; 95% CI, 0.74-1.19). Additionally, time to treatment discontinuation did not differ between the R-T and T-R groups (8.7 vs 8.1 months; HR, 0.91; 95% CI, 0.73-1.14).

There is a paucity of data surrounding sequencing as it relates to fruquintinib. Data are limited to 2 China-based studies, both of which support that regorafenib followed by fruquintinib may be associated with longer OS than the reverse.^{20,21} However, further confirmatory prospective trials are needed.

Impact of Hematologic Toxicities on Treatment Sequencing

Neutropenia, a reduced absolute neutrophil count commonly associated with myelosuppressive chemotherapy, remains a significant burden on both patients being treated for cancers and for health care systems. FN, a severe form of neutropenia, is considered an oncologic emergency; it occurs in 7.8 per 1000 patients with cancer in the US.²² These chemotherapy-related neutropenic and FN events impose a substantial impact on patients in terms of mortality and hospitalizations and on health care systems in terms of costs.

As patients and physicians navigate the progression of mCRC, the burden of these AEs becomes more pronounced. Myelosuppression creates challenges to administering additional chemotherapy (eg, FTD/TPI alone or with bevacizumab) immediately after previous use of intensive lines of therapy that also have caused bone marrow toxicity.²³ Exposure to multiple lines of chemotherapy can lead to residual bone marrow injury (ie, hematologic toxicities including neutropenia, anemia, and/or thrombocytopenia) and cumulative neurotoxicity that can affect QOL and overall patient outcomes.^{24,25} In a survey of patients with prior exposure to chemotherapy, a moderate to major overall impact on QOL due to myelosuppression and related AEs was reported by 88% of respondents.

Maintaining QOL has emerged as a valued treatment goal as revealed in a survey of over 600 physicians—34% cited QOL as their foremost objective for mCRC patients in the 3L setting.²⁶ It is also important to explore strategies that mitigate the additive bone marrow suppression associated with chemotherapeutic regimens.²³ Incorporating therapies with alternative mechanisms of action may achieve this objective and ensure that all potentially active agents remain available to patients.

Both regorafenib and fruquintinib are associated with low rates of hematologic toxicity, as previously discussed.^{10,11} It is important to note that both of these therapies are associated with other nonhematologic toxicities, such as HFSR and fatigue, that will also have an impact on QOL.^{10,12,27,28} Close patient monitoring is still needed to manage these nonhematologic toxicities, minimize impact to QOL, and maximize clinical benefit of treatment.⁵ Dose optimization and/or modifications of either regorafenib or fruquintinib may be necessary to address treatment-related toxicities while preserving patient QOL. Such modifications are key to ensuring that the benefits of treatment are realized without compromising the patient's overall well-being.⁵

Economic Considerations

The economic landscape of mCRC treatment extends beyond the costs of therapies themselves; it encompasses a spectrum of expenses associated with the AE profiles of treatments, including

hematologic toxicities (eg, neutropenia), which is a major cost driver for patients with mCRC.²⁹ These considerations are crucial when evaluating the overall economic impact of different therapeutic options for mCRC.²² Cancer-related neutropenia, which includes neutropenia related to chemotherapy, can impose a significant economic burden on health care systems and patients. Overall cost includes direct costs such as expenses associated with hospitalizations and indirect costs from loss of productivity.

A study published in 2017 examined 2012 data from the National Inpatient Sample and the Kids' Inpatient Database of the Healthcare Costs and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality as they relate to chemotherapy-induced neutropenia.³⁰ *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes were used to identify cancer-related neutropenia hospitalizations. For analysis, inpatient stays with a diagnosis of primary or secondary cancer and of neutropenia or fever with undetermined cause were selected. Costs (2012 US\$) were calculated by converting hospital charges to costs using HCUP cost-to-charge ratios as designated by the Centers for Medicare & Medicaid Services.

Investigators identified more than 91,000 cancer-related hospitalizations for neutropenia among adults and almost 17,000 more among children, accounting for 5.2% of all cancer-related hospitalizations among adults and 22.7% among children.³⁰ Hospitalizations for cancer-related neutropenia in adults were longer (by 2.7 days) and more costly (by \$5685) than for conditions not related to neutropenia. The estimated mean hospital costs per stay were \$14,278 for adult patients with cancer of the rectum or anus and \$15,431 for adult patients with colon cancer, totaling over \$70 million for hospitalizations related to neutropenia in adult patients with CRC in 2012. Neutropenia-related hospitalizations in cancer patients accounted for 5.2% of all cancer-related hospitalizations and for 8.3% of all cancer-related hospitalization costs. These results highlight the disproportionate burden to health systems and costs associated with the potentially life-threatening occurrence of cancer-related neutropenia.

A 2022 expert review examined studies published between 2015 and 2020 that reported on the burden of chemotherapy-induced FN in terms of hospitalization, mortality, and cost.²² Among adults with solid tumors hospitalized for neutropenia or FN, mortality ranged between 2.6% and 7.0%. Risk factors for mortality included older age, admission to intensive care, and presence of comorbidities or other diagnoses such as infection, sepsis, or pneumonia.

A retrospective, open-cohort study of medical and pharmacy claims from the first quarter of 2009 to the second quarter of 2014 identified 4158 patients with a diagnosis of mCRC and more than 1 claim (prescription or administration) of more than 1 recommended mCRC treatment.²⁹ Of these, 2261 patients (54.4%) had a 2L treatment, and 1115 (26.8%) had a 3L treatment. On average

(SD), each patient had 2.1 (1.4) episodes of mCRC treatment, with each treatment episode lasting a mean (SD) of 166 (144) days.²⁹ The occurrence of AEs was high and was associated with substantial economic burden. During the 1L treatment episode, 90% of patients experienced 1 or more AE, and AE rates remained high in the 2L and 3L (85% and 86%, respectively).

Reported monthly total costs were significantly higher for patients who experienced 1 or more AEs in the cardiovascular, central nervous system, endocrine or metabolic, hematologic, and respiratory categories compared with those who did not experience AEs in that same category. Hematologic AEs were the costliest, followed by those affecting respiratory, endocrine or metabolic, and central nervous systems.²⁹ Specifically, after adjustment of the model for differences in patient baseline characteristics, the adjusted monthly total costs for patients with hematologic AEs were \$19,115 and for those with AEs that were not hematologic were \$17,209—a significant difference of \$2289 ($P < .05$). In addition, patients with hematologic AEs during treatment episodes often had other types of AEs, resulting in higher health care costs than noted among patients with nonhematologic AEs.

To date, there is no US-based cost-effectiveness study of real-world data that incorporates all of the aforementioned 3L therapies, particularly one that includes fruquintinib. However, in a 2022 study, Cho et al used a Markov model to evaluate the relative cost-effectiveness of 4 treatment options for mCRC based on an assessment of benefits, toxicities, and cost of care.³¹ The treatment regimens evaluated were regorafenib standard dosing (RSD) of 160 mg once daily orally; regorafenib initiated at 80 mg once daily and escalated weekly in 40-mg increments up to 160 mg once daily, as tolerated (ReDOS); FTD/TPI; and FTD/TPI plus bevacizumab. Relative cost effectiveness was evaluated using quality-adjusted life-years (QALYs). This evaluation included a comparison of costs for AEs across each therapy regimen based on data reported in the pivotal trials for each regimen.

Costs associated with AE management were lowest with the RSD and ReDOS regimens (\$5715 and \$9008, respectively).³¹ AE-related costs for managing the FTD/TPI and FTD/TPI plus bevacizumab regimens were more than twice as high as were those associated with RSD (\$15,160 and \$17,179).

Costs of AE management have not been incorporated as factors in provider and health-system assessments of treatment regimens for advanced, incurable cancers. It is also acknowledged that additional cost-effectiveness data are needed to better understand how fruquintinib fits into this landscape. Still, the results of studies discussed here provided cost information that can be associated with AE management and put particular emphasis on costs related to myelosuppression and other toxicities. Incorporating cost of AE management into the development of treatment pathways should be considered.

Managed Care Considerations

While 3L+ treatment options continue to expand, there is a lack of comparative trials. This lack of evidence-based guidance regarding the most effective sequencing for mCRC therapies adds to the complexity of treatment decision-making that would be most appropriate for individual patients.¹⁸ To address this knowledge gap, there is a pressing need for data that can further elucidate the intricacies of treatment sequencing. Such studies are essential to guide informed decision-making for health care providers and managed care organizations.

Formal pathways or guidelines lack direct guidance on optimal treatment sequencing in mCRC; instead, they provide a variety of treatment sequencing strategies. In the absence of standardized guidance, health care plans and systems can derive relevant data based on real-world comparative effectiveness evaluations.⁸ This flexibility enables health care entities to adapt to the unique needs of their patient populations and ensure that treatment decisions are evidence-based and patient-centered.

The future development of real-world and head-to-head data will play a pivotal role in informing appropriate utilization management strategies. As patients reach later lines of treatment, these strategies will be instrumental in optimizing the selection and sequencing of therapies. Managed care organizations will need to be proactive in leveraging emerging data to tailor treatment approaches effectively while managing costs and ensuring that patients receive the most suitable care based on their clinical status and history.

Conclusion

With an expanding landscape of treatment options, the need for well-informed sequencing strategies in 3L+ treatments is becoming increasingly crucial for patients with mCRC. Four FDA-approved 3L+ treatment options currently exist in the United States including regorafenib, FTD/TPI alone or with bevacizumab, and fruquintinib.^{10,15} With these new approvals, no singular treatment sequence is recommended above others by the NCCN Guidelines.⁸ The future development of well-designed comparative studies between approved treatment sequences may aid in clinical decision-making and help address the unanswered questions surrounding sequencing.

Striking a balance between the patient's QOL and the effectiveness of treatment is also crucial. Addressing the risk of toxicities including neuropathy and myelosuppression is crucial to improve overall outcomes.^{22,24}

In light of these challenges and opportunities, the treatment landscape for 3L+ mCRC is evolving. As new therapies continue to emerge and more data become available, the medical community can strive towards a more personalized, effective, and patient-centered treatment strategy. Achieving a balance between cost effectiveness, toxicity, efficacy, and QOL remains the ultimate goal for optimizing patient outcomes in this complex therapeutic landscape of mCRC. ■

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