Case Study Series

Clinical Advances in Hematology & Oncology October 2025

Applying FRESCO Trial Insights in Real-World Management of mCRC

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MILLENNIUM MEDICAL PUBLISHING, Inc.

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine (PubMed/MEDLINE) and EMBASE

INDICATION

FRUZAQLA® (fruquintinib) is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy.

SELECTED IMPORTANT SAFETY INFORMATION

FRUZAQLA is associated with Warnings and Precautions related to: Hypertension, Hemorrhagic Events, Infections, Gastrointestinal Perforation, Hepatotoxicity, Proteinuria, Palmar-Plantar Erthrodysesthesia (PPE), Posterior Reversible Encephalopathy Syndrome (PRES), Impaired Wound Healing, Arterial Thromboembolic Events, Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF), Embryo-Fetal Toxicity, and Adverse Reactions.

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In the Clinic . . .

AK is a 56-year-old woman with no children who lives independently. Her medical history is notable only for episodic migraines; she has no significant comorbidities and maintains a good functional status. She initially presented to a gastroenterologist with right upper quadrant abdominal pain, unintentional weight loss, and altered bowel habits.

Colonoscopy identified a high rectal lesion, which was confirmed on histopathologic evaluation as rectal adenocarcinoma (T3N1). Computed tomography (CT) of the chest/abdomen/pelvis revealed synchronous liver metastasis, consistent with a clinical diagnosis of stage IV disease. Molecular profiling of the tumor performed via next-generation sequencing demonstrated that it was microsatellite stable (MSS) and harboring a *KRAS* G12V mutation. Overall, she is considered to have excellent performance status.

Following review at an external multidisciplinary tumor board, the patient initiated systemic therapy with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus bevacizumab, achieving partial radiographic response in both the primary rectal lesion and hepatic metastases. She subsequently received short-course pelvic radiation, resulting in further reduction of the primary tumor. Serum carcinoembryonic antigen (CEA) declined from 250 ng/mL to 10 ng/mL. This was followed by surgical management, which included low anterior resection and concurrent right hepatectomy. Postoperatively, she completed an additional 3 months of adjuvant FOLFOX. She remained in complete remission.

At routine follow-up 6 months post-treatment, AK's CEA rose to 55 ng/mL. Imaging revealed bilateral, unresectable pulmonary nodules without hepatic recurrence. She subsequently established care at our practice.

Second-line therapy with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab was initiated. After 4 cycles, imaging demonstrated partial regression of lung lesions and CEA declined to 44 ng/mL. However, irinotecan-associated diarrhea exacerbated by prior low anterior resection significantly impaired her quality of life (QOL). Dose reduction was followed by administration of 4 additional cycles. Despite this, CEA levels began to rise and imaging showed slight progression of pulmonary disease.

In light of disease recurrence, treatment options were re-evaluated. The patient was ineligible for anti–epidermal growth factor receptor (anti-EGFR) therapy owing to *KRAS* mutation and ineligible for immunotherapy given her MSS status. She reported persistent fatigue, anorexia, and FOLFOX-associated neuropathy, although diarrhea had resolved.

Given her desire to improve daily functioning, treatment goals were revised from remission to disease control and QOL improvement. Although she was not eligible for clinical trials at the time, a treatment pause was considered to optimize future trial candidacy. This led to a discussion of nonchemotherapy third-line treatment options, and fruquintinib was initiated at 5 mg daily, administered on a 21/28-day cycle.

Overview of mCRC

Colorectal cancer (CRC) is the second deadliest cancer in the United States, accounting for an estimated 52,900 deaths in 2025.[1,2] Although historically considered a disease of older adults, its incidence and mortality rates have been rising concerningly among younger adults.[1,2]

Metastases are common in patients with CRC, with the liver being the most prevalent site, followed by the thorax.[3] More than 70% of patients with CRC experience metastatic disease (metastatic CRC [mCRC]), occurring either at diagnosis (approximately 23%) or disease progression over the course of treatment (up to 50%).[1,4]

The 5-year relative survival for patients diagnosed with CRC is 65.4%.[1] However, it is significantly impacted by disease stage; patients with mCRC have a dismal 5-year relative survival rate of 16.2%.[1] This is in large part owing to the declining length of progression-free survival (PFS) that patients experience as they progress through various lines of treatment, reported in 1 study as decreasing from 8.5 months (range, 4-23) in the first line to 5 months (range, 4-7.5) in the second line and 3 months (range, 2-5.5) in the third line.[5] There is a clear unmet need for treatments to prolong the duration of PFS.

Therapeutic Options in mCRC

The treatment landscape for mCRC has undergone several notable changes over the past few decades.

The use of 5-fluorouracil (5-FU) for the treatment of CRC can be traced to the late 1950s.[6] Over subsequent decades, treatment options for CRC were primarily limited to the addition of the reduced folate leucovorin.[6] A meta-analysis published in 2004 reported that the combination of 5-FU plus leucovorin provided improved tumor response rates but had only a modest benefit on overall survival (OS) in mCRC.[7]

During the 2000s, the topoisomerase I inhibitor irinotecan and the platinum agent oxaliplatin became available.[6] These agents formed the basis of the FOLFOX and FOLFIRI combination chemotherapy regimens, which demonstrated similar benefit in PFS, time to progression, and OS between the 2 regimens in the GOIM (Gruppo Oncologico dell'Italia Meridionale) and GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) studies.[6] Subsequently, the 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) regimen was shown to achieve improved efficacy but at the cost of increased toxicity.[6] The 2000s also saw the introduction of capecitabine (an oral 5-FU prodrug) to treat mCRC, which was associated with improved efficacy outcomes compared with 5-FU plus leucovorin.[6]

Another important advancement in the early 2000s was the introduction of agents that inhibited either the vascular endothelial growth factor (VEGF) or EGFR pathways.[6] Pivotal studies demonstrated significant improvements in OS and PFS in the first-line setting with the addition of the anti-VEGF antibody bevacizumab (and later, aflibercept and the VEGF receptor inhibitor ramucirumab) to chemotherapy compared with chemotherapy alone.[6,8] Similarly, superior OS and PFS in the first-line setting were observed with the addition of the anti-EGFR antibodies cetuximab or panitumumab.[6,8] Importantly, the anti-EGFR agents were the first to show specificity for the molecular characteristics of the tumor, with efficacy primarily limited to mCRC harboring wild-type *KRAS*.[6]

With growing insight into the molecular landscape of mCRC, multiple targeted agents have been approved since 2016 for tumors harboring actionable mutations.[9] Additionally, the identification of microsatellite instability-high, deficient mismatch repair (dMMR), and POLE/POLD1 polymerase mutations has enabled the use of these biomarkers to select patients for immune checkpoint inhibitor therapy.[10] However, most patients with mCRC have tumors that do not harbor actionable mutations or dMMR status, and therefore do not benefit from these options.[11]

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

Credit: Ziad M. El-Zaatari/Science Source

Post–Standard Therapy Third-Line Options for Patients With mCRC Without Targetable Mutations

Treatment of patients who progressed on standard oxaliplatin- and irinotecan-based regimens was limited to salvage chemotherapy with agents such as capecitabine, raltitrexed, mitomycin C, and gemcitabine, with minimal benefit observed in clinical trials.[9] This approach changed with the approval of regorafenib in 2012, followed in 2015 with the approval of trifluridine/tipiracil.[12,13] However, after these approvals, there was a pause in the approval of agents specifically for patients regardless of mutation status until 2023, when fruquintinib was approved.[9,14]

There are 3 drugs approved by the US Food and Drug Administration in the third-line post–standard therapy for patients with mCRC without targetable mutations: regorafenib, trifluridine/tipiracil with or without bevacizumab, and fruquintinib (Figure 1). They are all indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy.[12-14] For trifluridine/tipiracil, this indication applies to its use as a single agent or in combination with bevacizumab.[13]

The pivotal trials supporting these indications were similarly designed, phase 3, placebo-controlled trials (the trifluridine/tipiracil combination with bevacizumab was compared with trifluridine/tipiracil alone).[15-21] All studies were conducted in patients with treatment-refractory mCRC, with large populations evaluated.[15-21]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend all 4 regimens for patients who are ineligible for or who have progressed on checkpoint inhibitor immunotherapy and have progressed through all available regimens.[10] All 4 regimens have a NCCN Category 2A recommendation, and the guidelines note that, for trifluridine/tipiracil, the combination with bevacizumab is preferred over trifluridine/tipiracil alone.[10] *Note that NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.*

MOA Considerations

The VEGF pathway plays a key role in tumor angiogenesis.[22] This pathway is triggered by binding of VEGF to 3 tyrosine kinase receptors: VEGFR-1, VEGFR-2, and VEGFR-3.[22] Binding of VEGF activates the receptors and induces phosphorylation of the kinase domain, leading to the activation of intracellular signaling pathways that culminate in angiogenesis (VEGFR-1 and VEGFR-2) and lymphangiogenesis (VEGFR-3).[22]

Fruquintinib is a nonchemotherapy tyrosine kinase inhibitor (TKI) that inhibits all 3 VEGFRs, restricts tumor growth and progression, with the potential to inhibit lymphangiogenesis.[22] Unlike other VEGFR inhibitors, such as sunitinib, sorafenib, regorafenib, and pazopanib, fruquintinib achieves VEGFR inhibition with limited off-target kinase activity.[22] Fruquintinib limits off-target kinase activity, allowing for drug exposure achieving sustained target inhibition.[23]

In contrast, regorafenib is a multitargeted TKI.[12] In addition to inhibition of VEGFR-1, -2, and -3, regorafenib has been shown in preclinical studies to inhibit the activity of RET, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl, and CSF1R at concentrations that have been achieved clinically.[12]

Unlike regorafenib and fruquintinib, trifluridine/tipiracil is not a TKI but instead consists of a thymidine-based nucleoside analogue (trifluridine) and the thymidine phosphorylase inhibitor (tipiracil).[13] Tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase; trifluridine is incorporated into DNA, interferes with DNA synthesis, and inhibits cell proliferation.[13] Bevacizumab is designed to directly bind to VEGF extracellularly to prevent interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells.[24]

Pivotal Trials

Regorafenib was approved based on the phase 3 CORRECT[15] and CONCUR[16] trials, which enrolled 760 and 204 patients, respectively. In the CORRECT trial, median OS was 6.4 vs 5.0 months (hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; *P*=.0052), and median PFS was 1.9 vs 1.7 months (HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001).[15] In the CONCUR trial, median OS was 8.8 vs 6.3 months (HR, 0.55; 95% CI, 0.40-0.77; *P*=.00016), and median PFS was 3.2 vs 1.7 months (HR, 0.31; 95% CI, 0.22-0.44; *P*<.0001).[16] Grade 3 or higher adverse events (AEs) occurring in 5% or more of patients in the regorafenib arm included hand-foot skin reaction (HFSR; 17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash/desquamation (6%) in CORRECT, and HFSR (16%), hypertension (11%), elevated alanine aminotransferase (ALT; 7%), and elevated aspartate aminotransferase (AST; 6%) in CONCUR.[15,16]

Trifluridine/tipiracil was approved based on the phase 3 RECOURSE[17] and TERRA[18] trials, which enrolled 800 and 406 patients, respectively. In the RECOURSE trial, median OS was 7.1 vs 5.3 months (HR, 0.68; 95% CI, 0.58-0.81; *P*<.001), and median PFS was 2.0 vs 1.7 months (HR, 0.48; 95% CI, 0.41-0.57; *P*<.001).[17] In the TERRA trial, median OS was 7.8 vs 7.1 months (HR, 0.79; 95% CI, 0.62-0.99;

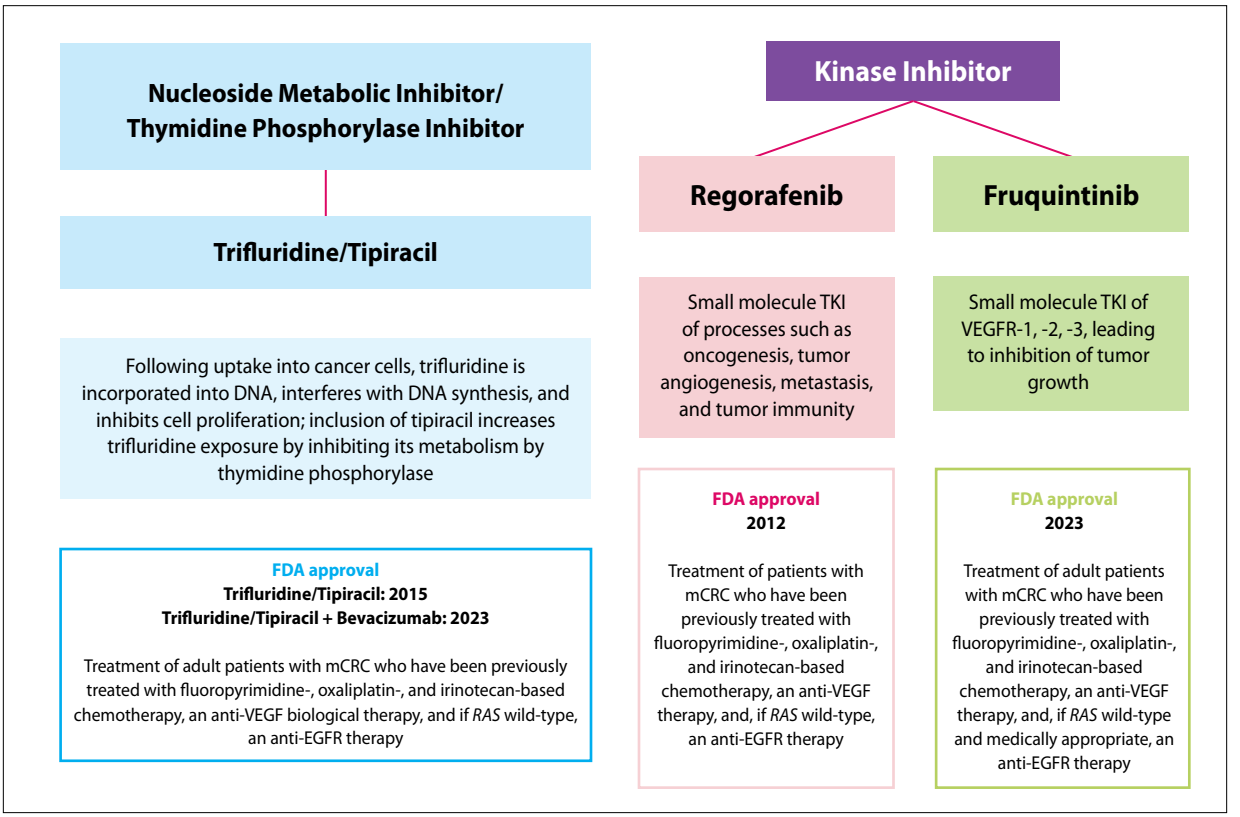


Figure 1. Post–standard therapy agents used in the third line for the treatment of mCRC with no targetable mutations.[12-14]

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

P=.035), and median PFS was 2.0 vs 1.8 months (HR, 0.43; 95% CI, 0.34-0.54; *P*<.001).[18] Grade 3 or higher AEs occurring in 5% or more of patients in the trifluridine/tipiracil arm included neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (5%) in RECOURSE, and neutropenia (33.2%), leukopenia (20.7%), anemia (17.7%), lymphopenia (14.4%) in TERRA.[17,18]

Trifluridine/tipiracil plus bevacizumab approval was based on the SUNLIGHT[19] trial, which compared trifluridine/tipiracil plus bevacizumab with trifluridine/tipiracil in 492 patients. The median OS was 10.8 vs 7.5 months (HR, 0.61; 95% CI, 0.49-0.77; *P*<.001) and median PFS was 5.6 vs 2.4 months (HR, 0.44; 95% CI, 0.36-0.54; *P*<.001).[19] Grade 3 or higher AEs occurring in 5% or more of patients in the test arm included neutropenia (43.1%), anemia (6.1%), and hypertension (5.7%).[19]

Fruquintinib: A Closer Look

In 2023, fruquintinib was approved for the treatment of adult patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy.[14] This approval was based on the results of 2 clinical trials: FRESCO-2 and FRESCO (Table 1).[14]

Clinical Trials: FRESCO and FRESCO-2

FRESCO was a phase 3 study conducted in patients with mCRC who had received 2 or more prior lines of chemotherapy.[20] Compared with placebo, treatment with fruquintinib resulted in significant improvement in OS (median OS, 9.30 vs 6.57 months; HR, 0.65; 95% CI, 0.51-0.83; *P*<.001) and PFS (median PFS, 3.71 vs 1.84 months; HR, 0.26; 95% CI, 0.21-0.34; *P*<.001).[20] Based on these results, fruquintinib gained approval in China.[21] However, at the time that the FRESCO study was conducted, in China neither VEGF pathway inhibitors nor EGFR pathway inhibitors were routinely used as part of the standard of care treatment for mCRC; additionally, neither regorafenib nor trifluridine/tipiracil was available.[21] Therefore only a minority of patients had received a VEGF inhibitor (30%) or EGFR inhibitor (14%) prior to receiving fruquintinib, and no patients had any prior

treatment with regorafenib or trifluridine/tipiracil.[21]

Thus FRESCO-2 was designed as an international, randomized, double-blind, placebo-controlled, phase 3 study conducted across 14 countries in North America, Europe, Asia, and Australia.[21] The study enrolled a heavily pretreated population of adult patients with mCRC who were eligible only if they had received all standard treatments, including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if *RAS* wild-type), and had disease progression on or been intolerant to trifluridine/tipiracil or regorafenib.[21] A total of 691 patients were randomized 2:1 to receive either fruquintinib (n=461) or placebo (n=230); patients in both arms also received best supportive care.[21]

In the overall population of patients, the median age was 64 years (IQR, 56-70), and 72% had liver metastasis.[21] A total of 63% of the population had a tumor harboring a *RAS* mutation.[21] Patients had a median of 4 prior lines of treatment for metastatic disease, and 73% had received more than 3 prior lines of therapy.[21] The vast majority of the population (96%) had received prior anti-VEGF therapy, and 39% had received prior anti-EGFR therapy.[21] All patients had been treated with trifluridine/tipiracil (52%), regorafenib (8%), or both (39%).[21]

The primary endpoint of FRESCO-2, OS, was met in the fruquintinib arm vs placebo (median OS, 7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; *P*<.0001).[21] PFS was a key secondary endpoint, and was also significantly improved with fruquintinib compared with placebo (median PFS, 3.7 vs 1.8 months; HR, 0.32; 95% CI, 0.27-0.39; *P*<.0001).[21]

Table 1. Fruquintinib: Summary of Pivotal Trials

	Trial	
	FRESCO[20]	**FRESCO-2[21]**
Comparator arm	Placebo	Placebo
Patients (N)	416	691
Median OS, months, HR (95% CI)	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)	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	Hypertension (21.2%), HFSR (10.8%)	Hypertension (14%), asthenia (8%), HFS (6%)

AEs, adverse events; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Dosing and Administration

The recommended dose of fruquintinib is 5 mg orally once daily, administered for the first 21 days of each 28-day cycle.[14] In my experience, this schedule of 3 weeks on and 1 week off is relatively easy for patients to understand and follow. Additionally, fruquintinib can be administered either with or without food, and is taken at approximately the same time each day.[14]

The recommended starting dose can be modified as needed for adverse reactions, with the first and second dose reductions recommended to 4 mg and 3 mg, respectively.[14] If a patient is unable to tolerate the 3 mg dose, then fruquintinib should be permanently discontinued.[14]

In most cases, grade 3 adverse reactions are managed with a temporary withholding of fruquintinib and resumption at a reduced dose upon resolution to grade 1 or lower.[14] An exception to this is hemorrhagic events, which require a dose reduction at grade 2 and discontinuation at grade 3.[14] Generally, fruquintinib should be discontinued with grade 4 adverse reactions, although in some cases of non–life-threatening toxicity, resumption at a lower dose may be considered.[14]

Managing Potential Side Effects

The rates of adverse reactions reported in the FRESCO-2 trial are shown in Table 2. Dose interruption because of AEs was experienced by 47% of fruquintinib-treated patients (vs 27% in the placebo arm).[21] Dose reductions because of AEs were reported in 24% of fruquintinib-treated patients (vs 4% of placebo-treated patients), most frequently owing to hand-foot syndrome (5%), hypertension (4%), and asthenia (4%).[21] Discontinuation because of AEs was similar between treatment arms (20% in the fruquintinib arm and 21% in the placebo arm). Asthenia (2%) was the most frequent reason for fruquintinib discontinuation.[21]

In FRESCO, dose interruption because of AEs was experienced by 35.3% of fruquintinib-treated patients (vs 10.2% in the placebo arm).[20] Dose reductions because of AEs were reported in 24.1% of fruquintinib-treated patients (vs 4.4% of placebo-treated patients).[20] Discontinuation because of AEs occurred in 15.1% of fruquintinib-treated patients (vs 5.8% of placebo-treated patients), and was primarily owing to proteinuria.[20]

Hypertension

Hypertension was the most frequent AE reported with fruquintinib.[21] In a pooled safety population of 911

Table 2. Adverse Events Experienced by at Least 1 Patient in the Safety Population of the FRESCO-2 Study [21]

Adverse event, %	FRESCO-2 trial			
	Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99	63	93	50
Hypertension	37	14	9	1
Asthenia	34	8	23	4
Decreased appetite	27	2	17	1
Diarrhea	24	4	10	0
Hypothyroidism	<21	<1	<1	0
Fatigue	20	4	16	1
Hand-foot syndrome	19	6	3	0
Abdominal pain	18	3	16	3
Nausea	17	1	18	1
Proteinuria	17	2	5	1
Constipation	17	<1	10	0
Dysphonia	16	0	5	0
Stomatitis	15	2	3	<1
Vomiting	14	2	12	2
Mucosal inflammation	14	<1	3	0
Weight decrease	12	1	9	<1
Arthralgia	11	1	4	0
AST increase	11	2	5	1
ALT increase	10	3	4	<1
Back pain	10	1	7	1
Pyrexia	10	<1	10	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

fruquintinib-treated patients (from 3 randomized, placebo-controlled studies [which included FRESCO-2], 3 open-label studies, and an open-label lead-in cohort of FRESCO-2), the rate of hypertension was 49%, with 19% as grade 3 or 4 hypertensive events and 0.3% as hypertensive crisis.[14]

Hypertension has been identified as a class effect of VEGF inhibitors and is considered manageable with appropriate monitoring and antihypertensive therapy.[25] Treatment initiation with fruquintinib requires controlled baseline blood pressure followed by weekly monitoring during the first month, then monthly thereafter and as clinically indicated.[14] Additionally in our clinic, patients are required to record their blood pressure at the same time each day after sitting down for 5 minutes and communicate these values to the provider team. In the event of hypertension, antihypertensive therapy is either initiated or adjusted as needed.[14] Grade 3 hypertension warrants dose interruption and resumption at a reduced dose; grade 4 hypertension necessitates discontinuation of fruquintinib.[14]

Proteinuria

In the pooled safety population, proteinuria occurred in 36% of fruquintinib-treated patients, including 2.5% grade 3 or higher events, with median time to the first onset being 22 days.[14] Monitoring is recommended both prior to starting fruquintinib and then regularly thereafter.[14] In our clinic, patients' urine protein levels are checked at least once every 4 weeks, and more frequently if needed. Spot urine tests are performed, and in the case of elevated protein level, fruquintinib is withheld, followed by a 24-hour urine test. In patients with proteinuria of at least 2 g/24 hours fruquintinib should be withheld until proteinuria is either fully resolved or is less than 1 g/24 hours.[14] Upon recovery, fruquintinib should

be resumed at the next lower dose level. In cases where proteinuria does not recover to less than 1 g/24 hours, or if the patient develops nephrotic syndrome, fruquintinib should be permanently discontinued.[14]

Infections

Fruquintinib can increase the risk of infections, including fatal infections.[14] In the pooled safety population, the most common infections reported with fruquintinib were urinary tract infections (6.8%), upper respiratory tract infections (3.2%), and pneumonia (2.5%); fatal infections included pneumonia (0.4%), sepsis (0.2%), bacterial infection (0.1%), lower respiratory tract infection (0.1%), and septic shock (0.1%).[14] Although fruquintinib should be withheld for grade 3 or 4 infections, or worsening infection of any grade, it can be resumed at the same dose upon resolution of the infection.[14]

Hepatotoxicity

Reports of fruquintinib-induced liver injury have occurred.[14] In the pooled safety population, 48% of fruquintinib-treated patients experienced increased levels of ALT or AST, which included 5% grade 3 or higher events and 0.2% fatal events.[14] Monitoring of liver function tests (ALT, AST, and bilirubin) prior to initiation of fruquintinib, then periodically throughout treatment, is recommended.[14] Depending on the severity of hepatotoxicity, management includes either temporarily withholding fruquintinib and then reducing the dose, or permanently discontinuing it.[14]

Other Adverse Events

Fatigue was another common AE with fruquintinib in the FRESCO-2 study.[21] In our clinic, we inquire about the patient's fatigue levels during routine office visits. Management includes a dose hold followed by a dose reduction in patients with significant fatigue.[14]

Voice changes, or dysphonia, can occur with fruquintinib (16% in FRESCO-2), but generally are not clinically significant (no grade 3 or higher events reported in FRESCO-2).[21] Similarly, stomatitis and mucosal inflammation may occur (15% and 14% of any grade in the FRESCO-2 trial) but there are low rates of grade 3 or higher events (2% and <1%, respectively).[21]

Fruquintinib can also cause palmar-plantar erythrodysesthesia (PPE).[14] In the pooled safety population, PPE occurred in 35%, including 8% with grade 3 events, with a median time to first onset of 19 days from the first dose.[14] Management includes withholding fruquintinib and then resuming at the same or reduced dose based on PPE severity.[14]

Third-Line Treatment Selection in mCRC: Therapeutic Goals, Patient-Centered Considerations, and NCCN Guidelines®

Therapeutic goals of later-line treatment of mCRC are inherently multifactorial, encompassing both the prolongation of OS and the preservation or improvement of patient QOL.[26]

By the time patients reach third-line therapy, they have typically undergone several months of systemic treatment, including cytotoxic chemotherapy in both first- and second-line settings. As a result, they often present with cumulative toxicities such as bone marrow suppression, anorexia, and fatigue.[19] In this context, the use of additional cytotoxic agents may exacerbate these burdens. Nonchemotherapy alternatives, such as TKIs, may provide a favorable tolerability profile, providing disease control while allowing patients a reprieve from prior treatment-related toxicities.[21]

Importantly, even non–life-threatening AEs, such as hand-foot syndrome, which is characterized by burning and blistering of the extremities, can substantially impact a patient's ability to walk or function. Similarly, gastrointestinal toxicities like nausea, vomiting, and diarrhea, as well as fatigue, can significantly diminish the patient's QOL. These considerations are critical when selecting therapy.[27] In my experience, nonchemotherapy options have increased the likelihood of sustained treatment, which may not only enhance disease control but may also help preserve QOL over time—an outcome as important as survival itself in the later-line setting.

Another dynamic element to treatment planning is the rapidly evolving therapeutic landscape, with numerous novel agents currently under investigation.[28] This introduces the possibility that a new therapy may become available within months, potentially altering the disease trajectory of the patient. Consequently, maintaining patient health and functional status becomes paramount—not only for immediate disease control but also to preserve eligibility for future clinical trial participation, which often requires both adequate organ function and robust performance status.[26] Minimizing treatment-related toxicity and maximizing the likelihood of sustained disease control to ensure that patients remain alive and fit for subsequent therapeutic opportunities is therefore an important aspect of third-line treatment.

Therapeutic selection at the third-line stage, post–standard therapy, must be based on shared decision-making aligning with the patient's goals and preferences. Key considerations include patient's anticipated adherence to the dosing schedule, toxicity profile of the agent, and the potential impact on QOL. In relatively young patients with good performance status who are highly motivated

to achieve remission, it is essential to prioritize survival benefit while concurrently evaluating drug tolerability and its impact on daily functioning. If, however, tumor progression is expected to cause mortality, then delaying progression with an agent that has a manageable toxicity profile should confer a meaningful survival advantage. Fruquintinib exemplifies this paradigm, as demonstrated in the FRESCO-2 trial, which showed statistically significant improvements in both OS and PFS.[21]

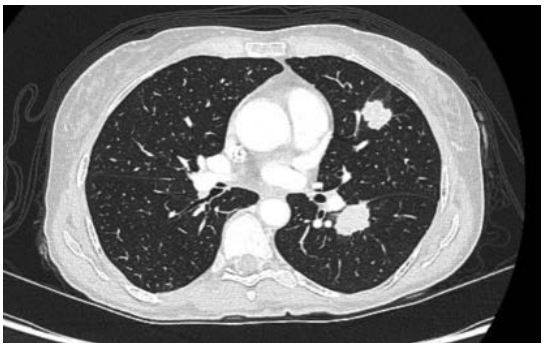
In the absence of head-to-head comparative studies of the available third-line therapeutic options post–standard therapy, each agent may be considered appropriate depending on the clinical context. This raises a critical question regarding their optimal sequencing. This decision is framed within the overarching goal of maximizing the duration a patient can tolerate treatment, thereby deriving the greatest possible benefit from each agent. NCCN Guidelines recommend fruquintinib as a potential treatment option for patients with prior exposure to oxaliplatin- and irinotecan-based regimens, regardless of tumor mutation status (category 2A).[10] The NCCN Guidelines further state that fruquintinib can be administered either before or after trifluridine/tipiracil or regorafenib, with no data available to inform the best order of these therapies.[10]

Monitoring Response to Treatment

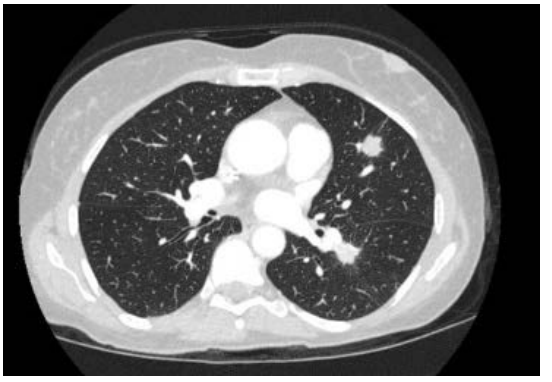
Symptom monitoring remains a clinically valuable tool for detecting disease progression and treatment-related toxicity in mCRC.[29] Close attention should be paid to the sites of metastasis and the specific symptoms being palliated, with ongoing assessment of whether palliation has been achieved.[29] However, symptom palliation alone may not reliably reflect treatment response, particularly in cases of indolent disease.[29]

Imaging is central to response assessment in mCRC.[30] In our practice, patients typically undergo imaging 8 weeks after treatment initiation, followed by imaging every 8 to 12 weeks during the first year. This schedule is generally effective for TKIs, including fruquintinib, especially in patients who are minimally symptomatic at baseline. Imaging typically relies upon CT scans of the chest/abdomen/pelvis with contrast, although magnetic resonance imaging may also be used.[31]

Tumor biomarkers offer valuable insights. Serial CEA monitoring is recommended, and, in our practice, CEA and carbohydrate antigen 19-9 are assessed at least every 4 weeks. Circulating tumor DNA (ctDNA), evaluated via liquid biopsy, is an emerging tool for response assessment.[32] A meta-analysis of 92 studies concluded that ctDNA is a reliable measure of response to systemic therapy, and that rising ctDNA levels may precede radiological recurrence.[33]



After 2 lines of standard therapy



After 2 months of fruquintinib as third-line therapy post–standard therapy

Figure 2. Computed tomography scan of the patient case, showing a reduction in lung nodule size with fruquintinib.

Back to the Clinic . . .

Following initiation of fruquintinib, the patient's CEA levels declined to below normal. She experienced mild fatigue toward the end of cycle 1, which resolved during the off-treatment week, suggesting treatment-related etiology. Given her biomarker response and clinical recovery, the dose was reduced to 4 mg once daily on the same schedule, which she tolerated well. Imaging at 8 weeks showed further reduction in lung nodules (Figure 2), consistent with stable disease. At 6 months, CT revealed slight nodule enlargement and a modest rise in CEA. Although still classified as stable disease, we initiated a search for clinical trial options, and she was deemed eligible based on her sustained recovery.

Bringing It All Together

The patient, AK, initiated treatment with FOLFOX plus bevacizumab (first line) followed by second-line treatment with FOLFIRI plus bevacizumab. However, when her CEA levels started to increase again, and the lung nodules were slightly enlarged on imaging, there were many considerations in determining an appropriate third-line treatment.

She was a candidate for neither anti-EGFR inhibitor therapy owing to her *KRAS* mutation status nor immune checkpoint inhibitor therapy owing to her MSS status. She reported significant neuropathy tracing back to the FOLFOX treatment, and although she was no longer experiencing diarrhea, she remained anorexic and fatigued. She voiced her desire to regain some of her daily activity level. This led to a discussion of nonchemotherapy third-line treatment options, and shifting treatment goals from achieving remission to achieving disease control and preserving QOL. After discussing various options, treatment with fruquintinib was initiated at the recommended dose of 5 mg for 21 days out of a 28-day cycle.

AK's CEA levels declined to below normal, and her mild fatigue toward the end of cycle 1 was resolved during the off-treatment week. Given her biomarker response and clinical recovery, the dose was reduced to 4 mg once daily on the same schedule, which she tolerated well. Imaging at 8 weeks showed further reduction in lung nodules, consistent with stable disease. At 6 months, CT revealed slight nodule enlargement and a modest rise in CEA. Although still classified as stable disease, we initiated a search for clinical trial options, and she was deemed eligible based on her sustained recovery.

The diverse cohort of pretreated mCRC patient population in the FRESCO and FRESCO-2 phase 3 trials generally mirrors what happens in real-world clinical practice.[20,21] Though not powered to show a difference, subgroup analyses demonstrated consistent OS and PFS benefit from fruquintinib across age, performance status, race, *RAS* mutation status, primary tumor site, liver metastasis, and prior therapies.[20,21] Moreover, most AEs can be managed by dose withholding or dose reduction, as with fatigue in the patient case. These findings support fruquintinib's important place in the treatment landscape and potential to benefit previously treated mCRC patients. Given that there are no predictive biomarkers for fruquintinib response, treatment decisions are individualized, integrating clinical trial data, toxicity profile, QOL implications, and patient preferences.

Disclosures

Dr Dayyani is part of the speakers bureau of Astellas, Ipsen, BeOne, Takeda, and Sirtex, and consults for AstraZeneca, Eisai, Amgen, and Taiho.

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