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Fruquintinib as Third-Line Therapy in mCRC Without Targetable Mutations, Insights From the FRESCO and FRESCO-2 Trials: Switching Mechanism of Action in a Patient Experiencing Significant Toxicity on Chemotherapy

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About the Patient

JT is a 71-year-old male diagnosed with metastatic rectosigmoid adenocarcinoma (Table 1). Molecular testing of a biopsy specimen revealed microsatellite stable, *RAS* wild-type, *BRAF* V600E wild-type, HER2-negative and no other alterations.

JT initiated first-line therapy with leucovorin, 5-fluorouracil (5-FU), and irinotecan (FOLFIRI) plus panitumumab, to which he quickly achieved a near complete response and received up to 6 months of treatment. His treatment course was complicated within the first 2 months by development of a grade 2 rash on his face. Additionally, he developed diarrhea that rapidly worsened to grade 3, and neutropenia that also became grade 3. These toxicities ultimately necessitated a dose reduction of irinotecan. He maintained treatment with 5-FU and panitumumab, which he continued for the next 4 months until a laboratory workup revealed grade 3 hypomagnesemia.

In the face of these accumulating toxicities, JT requested a drug holiday, which continued for approximately 4 months while he maintained stable disease, until a computed tomography (CT) scan showed tumor progression. At that point, he initiated second-line treatment with leucovorin, 5-FU, and oxaliplatin (FOLFOX) plus bevacizumab, but developed grade 3 neutropenia and thrombocytopenia after the first cycle, prompting a 25% dose reduction of the FOLFOX regimen. Although his disease showed a partial response, he expressed dissatisfaction with his treatment and an inability to maintain his quality of life. Additionally, imaging revealed disease progression after 4 months.

Next-generation sequencing was performed on a liquid biopsy, which confirmed persistent *RAS* mutations. Based on this, it was discussed with JT that he did not qualify for an anti–epidermal growth factor receptor (anti-EGFR) treatment rechallenge. With his prior cytopenias and preference for oral medications, we instead discussed switching to a noncytotoxic therapy option given his prior cytopenias. We proceeded to switch him to fruquintinib. Baseline testing revealed he was slightly hypertensive, so he was referred to his primary care physician, who initiated him on metoprolol and continued to monitor him at regular intervals. While on fruquintinib, he experienced hand-foot syndrome, which was well controlled and did not progress past grade 1. After 10 months, JT remains on fruquintinib, and his disease continues to remain stable with no progression on CT scans every 8 weeks.

Overview of mCRC

In 2026 alone, 158,850 new cases of colorectal cancer (CRC) are estimated to be diagnosed in the United States.[1] Increasingly, CRC is being diagnosed in younger adults, with patients under 65 years comprising nearly one-half (45%) of

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

Credit: Ziad M. El-Zaatari/Science Source

Table 1. Patient Case Summary

71-year-old male diagnosed with metastatic rectosigmoid adenocarcinoma	
Molecular testing	MSS, *RAS* wild-type, *BRAF* V600E wild-type, HER2-negative and no other alterations
First-line therapy	FOLFIRI plus panitumumab • Tumor response: near CR • Treated for 6 months • Toxicities: grade 2 rash; grade 3 diarrhea; grade 3 neutropenia • Dose reduction of irinotecan
Maintenance post–first-line	5-FU and panitumumab • Continued for 4 months • Toxicity: grade 3 hypomagnesemia
Second-line therapy	FOLFOX plus bevacizumab • Tumor response: PR • Toxicities: grade 3 neutropenia, grade 3 thrombocytopenia • Dose reduction of FOLFOX • Tumor progression after 4 months
Third-line therapy	Fruquintinib • Maintained stable disease • Initiated antihypertensive therapy

5-FU, 5-fluorouracil; CR, complete response; FOLFIRI, leucovorin, 5-FU, irinotecan; FOLFOX, leucovorin, 5-FU, oxaliplatin; MSS, microsatellite stable; PR, partial response.

new diagnoses. Although the 5-year relative survival rate has gradually increased, it was estimated to be 65% in the period of 2015 to 2021. The expected mortality of CRC in 2026 is estimated to be 55,203, making it the second deadliest cancer, although it is the fourth most commonly diagnosed cancer (after breast, prostate, and lung cancers).

One of the reasons for the high mortality rate of CRC is its propensity for metastasis, with 7 out of 10 patients experiencing metastatic disease, occurring either at diagnosis (23%) or in disease recurrence following treatment (up to 50%).[2,3] The liver is a frequent target for CRC metastatic spread.[4] When present at initial diagnosis, metastatic CRC (mCRC) has a particularly poor prognosis, with a severely diminished 5-year relative survival rate of 16.2%.[2]

The standard treatment of mCRC in the first and second lines is based on the chemotherapy regimens FOLFOX and FOLFIRI, which combine 5-FU and leucovorin with either the platinum agent oxaliplatin or the topoisomerase I inhibitor irinotecan, respectively. The GOIM (Gruppo Oncologico dell'Italia Meridionale) and GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) studies established that these 2 regimens achieve similar efficacy outcomes, including in time to progression, progression-free survival (PFS), and overall survival (OS).[5] Alternatively, 5-FU and leucovorin can be replaced with capecitabine and added to oxaliplatin (CAPEOX) to achieve a regimen with similar efficacy and lower toxicity compared with FOLFOX.[6] A third regimen, FOLFOXIRI, which combines 5-FU, leucovorin, oxaliplatin, and irinotecan, is associated with further prolongation of PFS and OS but at the cost of higher rates of toxicity.

The first- and second-line standard treatments of mCRC were significantly improved with the addition of vascular endothelial growth factor (VEGF) pathway inhibitors (bevacizumab, aflibercept, or ramucirumab) and EGFR pathway inhibitors (cetuximab or panitumumab). In pivotal trials in first-line mCRC, significant improvements in OS and PFS were demonstrated with the addition of these agents to standard chemotherapy.[5,7] The efficacy of the anti-EGFR agents were further shown to be limited primarily to mCRC tumors harboring wild-type *KRAS*.

As patients with mCRC progress through multiple lines of therapy, there is a decline in the PFS interval between each subsequent line. In one retrospective study of 120 patients, the PFS interval was 8.5 months (range, 4-23) after first-line treatment; this decreased to 5 months (range, 4-7.5) and 3 months (range, 2-5.5) after second-line and third-line treatments, respectively.[8] This is clinically relevant, as PFS is considered a surrogate endpoint for OS in patients with mCRC. Thus, there is a need for treatments aimed to prolong the duration of PFS.

A number of alternative treatment options are available for the treatment of mCRC tumors harboring actionable mutations.[9] Immune checkpoint inhibitor therapy is also important in mCRC tumors that are characterized as microsatellite instability-high, mismatch repair deficient, or harboring *POLE*/*POLD1* polymerase mutations.[10] However, most patients with mCRC are not candidates for either targetable agents or immune checkpoint inhibitor therapy.

Issue of Chemotherapy-Associated Toxicity in mCRC Without Targetable Mutations

Chemotherapy remains an important component of

Table 2. Major Toxicities Associated With Chemotherapies Used in the Treatment of mCRC[11-16]

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.

treatment for mCRC, either alone or in combination with biologic agents such as anti-VEGF or anti-EGFR therapies. However, treatment benefit must be balanced against chemotherapy-associated toxicity (Table 2), which can affect quality of life, dose intensity, treatment duration, and overall patient management.

Common chemotherapy backbones in mCRC include fluoropyrimidines, oxaliplatin, and irinotecan. Fluoropyrimidines, such as 5-FU and capecitabine, are associated with gastrointestinal and mucocutaneous toxicities, including diarrhea, mucositis, nausea, anorexia, and hand-foot syndrome, particularly with capecitabine.[11-13] Myelosuppression may also occur, although it is often less prominent than with some other cytotoxic agents. Rare but clinically important toxicities include cardiotoxicity and severe toxicity related to dihydropyrimidine dehydrogenase deficiency, which can lead to excessive fluoropyrimidine exposure.[14,15]

Oxaliplatin is strongly associated with peripheral neuropathy, which can become persistent and dose-limiting.[16] Because neuropathy can interfere with daily function, oxaliplatin is often discontinued after a defined induction period, with continuation of maintenance therapy using a fluoropyrimidine with or without the biologic agent.

Irinotecan is commonly associated with diarrhea and myelosuppression.[17] Diarrhea may occur early, as part of an acute cholinergic syndrome, or later, when it can be more prolonged and clinically significant. Neutropenia can increase infection risk and may require dose modification, treatment delay, or supportive care.

Therapeutic Goals and Patient-Centered Considerations With Third-Line Treatment

The goals of treatment in patients who have reached third-line or later therapy for mCRC primarily focus on prolonging survival while maintaining or improving quality of life.[18] Patients at this stage have received several cycles of cytotoxic chemotherapies and other systemic agents of the first and second lines of treatment. As a result they often enter third-line treatment burdened with cumulative toxicities such as bone marrow suppression, anorexia, and fatigue. These patients may benefit from a break in cytotoxic treatments, opting instead for nonchemotherapy alternatives such as tyrosine kinase inhibitors (TKIs) that offer the potential for disease stabilization while extending survival. However, it is important to consider that these agents are not free from side effects; instead they are associated with a different and often manageable toxicity profile.

It is imperative that the selection of third-line treatment in patients with mCRC is made based on shared decision-making, considering the patient's goals and preferences. Other patient considerations include their potential difficulties with adherence to the dosing schedule, the toxicity profile of the agent and its overlap with the patient's existing comorbidities, and the potential impact on quality of life. Prolonging survival is an essential goal but should be carefully weighed against a drug's tolerability and its impact on the patient's daily activities. In some cases, disease stabilization together with a manageable toxicity profile can result in a meaningful survival advantage.

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

Three agents (regorafenib, trifluridine/tipiracil with or without bevacizumab, and fruquintinib) are approved by the US Food and Drug Administration for patients who progress following standard combination chemotherapy regimens in the first- and second-line settings (Figure 1).[19-21] All three have in common an indication for the treatment of patients with mCRC who have previously received fluoropyrimidine-, oxaliplatin-,

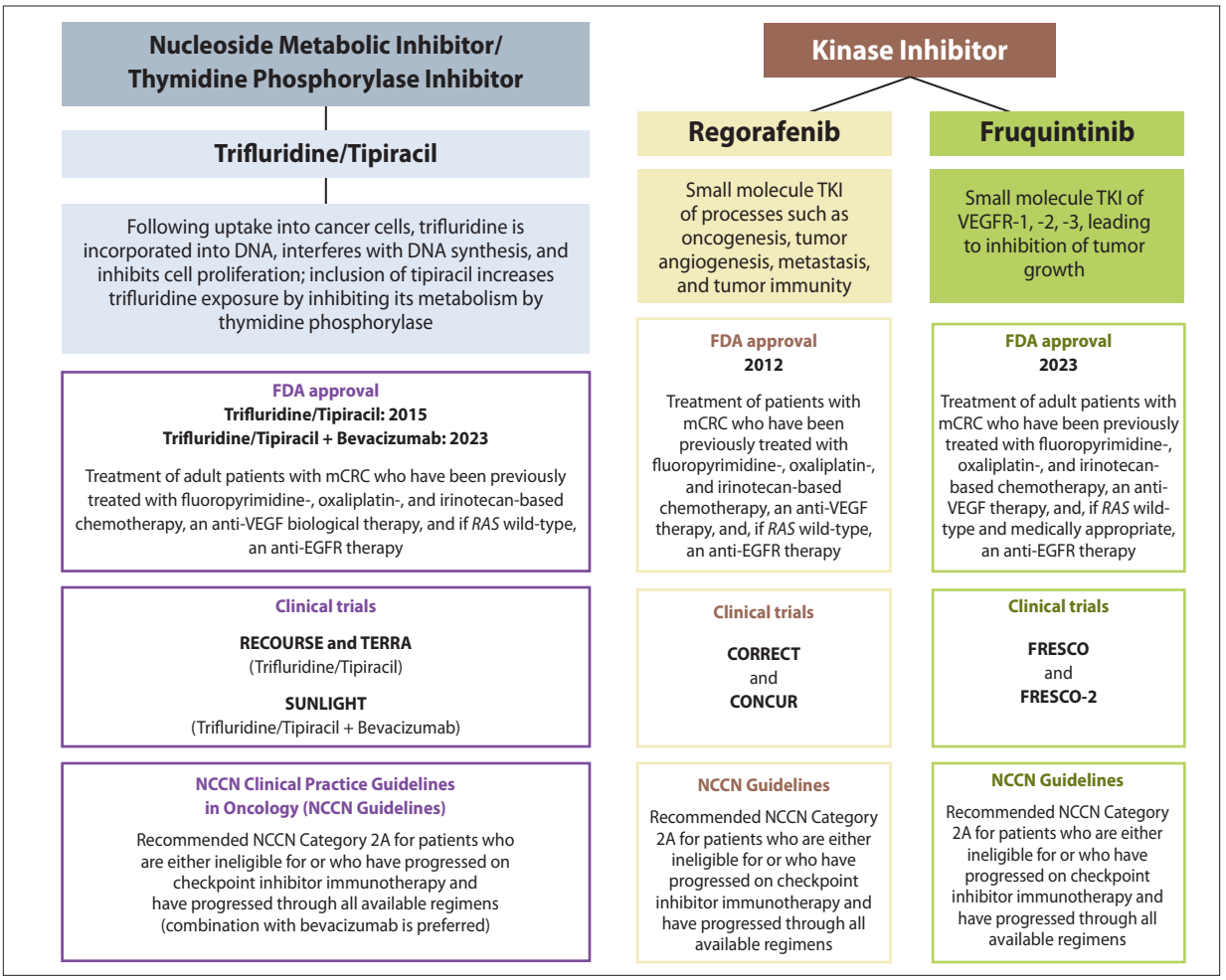

Figure 1. Post–standard therapy agents used in the third line for the treatment of mCRC with no targetable mutations.[10,19-21]

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.

and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy. In the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines), all 4 regimens have a Category 2A recommendation for patients who are ineligible for or who have progressed on checkpoint inhibitor immunotherapy and have progressed through all available regimens, although the combination of trifluridine/tipiracil with bevacizumab is preferred over trifluridine/tipiracil alone.[10]

Mechanism of Action

Regorafenib and fruquintinib are targeted therapies, whereas trifluridine/tipiracil is generally classified as an oral cytotoxic chemotherapy agent.

Regorafenib and fruquintinib are both TKIs that target the tyrosine kinase receptor for VEGF, of which three exist: VEGFR-1, VEGFR-2, and VEGFR-3.[19,21,22] When triggered by VEGF, activation of these receptors leads to intracellular signaling pathways that result in angiogenesis (VEGFR-1 and VEGFR-2) and lymphangiogenesis (VEGFR-3).[22] Because fruquintinib is a TKI active against all 3 VEGFRs, it is able to inhibit both the angiogenesis pathways to restrict tumor growth and progression, as well as lymphangiogenesis pathways. Fruquintinib inhibits VEGFRs with limited off-target kinase activity, allowing for drug exposure achieving sustained target inhibition.[22,23] In contrast, regorafenib is considered a multitargeted TKI, whereby in addition to all 3 VEGFRs, it inhibits the activity of several other kinases including 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.[19,22]

Trifluridine/tipiracil is not a TKI; instead it is a small molecule comprised of trifluridine (a thymidine-based nucleoside analogue) and tipiracil (a thymidine phosphorylase inhibitor).[20] Trifluridine becomes incorporated into

Table 3. Post–Standard Therapy Agents Used in the Third Line for the Treatment of mCRC With No Targetable Mutations: Summary of Pivotal Trials[24-31]

	Regorafenib			Trifluridine/ Tipiracil		Trifluridine/ Tipiracil + Bevacizumab	Fruquintinib	
Trial	CORRECT	CONCUR	ReDOS	RECOURSE	TERRA	SUNLIGHT	FRESCO	FRESCO-2
Comparator arm	Placebo	Placebo	Dose escalation	Placebo	Placebo	Trifluridine/ tipiracil	Placebo	Placebo
Patients, N	760	204	116	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	9.8 vs 6.0 0.72 (0.47-1.10) *P*=.12	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	2.8 vs 2.0 0.84 (0.57-1.24) *P*=.38	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%)	Abdominal pain (7%), HFSR (15%), fatigue (13%), hypertension (7%), increased AP (6%), hyponatremia (6%), colonic obstruction (6%)	Neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (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; AP, alkaline phosphatase; 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.

DNA, interfering with its synthesis and inhibiting cell proliferation; tipiracil increases trifluridine exposure via inhibiting its metabolism by thymidine phosphorylase.

Pivotal Trials of Regorafenib and Trifluridine/Tipiracil in mCRC

Fruquintinib, regorafenib, and trifluridine/tipiracil were all approved based on their efficacy and safety demonstrated in similarly designed, phase 3, placebo-controlled pivotal trials (Table 3).[24-31] The combination of trifluridine/tipiracil with bevacizumab was also evaluated in a phase 3 pivotal trial in which it was compared with trifluridine/tipiracil alone.[31] Each study enrolled relatively large populations of patients with treatment-refractory mCRC.

Regorafenib was evaluated in the 2 phase 3 pivotal trials CORRECT (760 patients) and CONCUR (204 patients), and in a practice-changing randomized phase 2 study ReDOS (116 patients) comparing standard regorafenib dosing with a dose-escalation strategy.[24-26] The international CORRECT trial enrolled patients from across North America, Europe, Asia, and Australia; thus the standard therapies patients had received as either first-line or second-line therapy were

required to include as many of the following as were licensed locally: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and either cetuximab or panitumumab (in patients with *KRAS* wild-type mCRC). Compared with placebo, regorafenib demonstrated significant improvements in both median OS (6.4 vs 5.0 months; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; *P*=.0052) and median PFS (1.9 vs 1.7 months; HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001).

The CONCUR study was designed to extend the findings from CORRECT into a population of Asian patients enrolled from China, Hong Kong, South Korea, Taiwan, and Vietnam. Because of this geographic limitation, the CONCUR study allowed patients to enroll who had not received a biologic agent (40% of the study population), which were not widely available across Asian countries at the time of the trial. In this population, regorafenib also showed significant improvements in median OS (8.8 vs 6.3 months; HR, 0.55; 95% CI, 0.40-0.77; *P*=.00016) and median PFS (3.2 vs 1.7 months; HR, 0.31; 95% CI, 0.220.44; *P*<.0001). Grade 3 or higher adverse events (AEs) reported by patients in the regorafenib arm of CORRECT included hand-foot skin reaction (HFSR; 17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash/desquamation (6%), and in CONCUR included HFSR (16%), hypertension (11%), elevated alanine aminotransferase (ALT; 7%), and elevated aspartate aminotransferase (AST; 6%).

ReDOS was a randomized phase 2 study comparing standard regorafenib dosing (160 mg once daily) with a dose-escalation strategy (80 mg, increasing to 120 mg during week 2 and 160 mg during week 3 based on the patient's tolerance and adverse events), both given 3 weeks on/1 week off. The dose-escalation arm significantly improved the likelihood of proceeding to cycle 3 (43% vs 26%; *P*=.043). Median OS favored dose escalation (9.8 vs 6.0 months; HR, 0.72; 95% CI, 0.47-1.10; *P*=.12), while median PFS was similar (2.8 vs 2.0 months; HR, 0.84; 95% CI, 0.57-1.24; *P*=.38). Grade 3/4 toxicities were generally lower with dose escalation, including fatigue (13% vs 18%), HFSR (15% vs 16%), and hypertension (7% vs 15%), except abdominal pain (17% vs 6%). These results were considered practice-changing and drive how regorafenib is currently administered in the clinic.

Like regorafenib, trifluridine/tipiracil was also evaluated in 2 pivotal phase 3 trials—the RECOURSE study (800 patients enrolled from the United States, Europe, Australia, and Japan) and TERRA (406 patients from across several Asian countries).[27,28] The median OS achieved in the RECOURSE trial was prolonged with trifluridine/tipiracil compared with placebo (7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58-0.81; *P*<.001), as was the median PFS (2.0 vs 1.7 months; HR, 0.48; 95% CI, 0.41-0.57; *P*<.001). In the TERRA trial, trifluridine/tipiracil also significantly prolonged median OS (7.8 vs 7.1 months; HR, 0.79; 95% CI, 0.62-0.99; *P*=.035) and median PFS (2.0 vs 1.8 months; HR, 0.43; 95% CI, 0.34-0.54; *P*<.001). Grade 3 or higher AEs reported by patients in the trifluridine/tipiracil arm of the RECOURSE trial included neutropenia (38%), leukopenia (21%), anemia (18%), and thrombocytopenia (5%), and of the TERRA trial included neutropenia (33.2%), leukopenia (20.7%), anemia (17.7%), and lymphopenia (14.4%).

A third trial, SUNLIGHT, compared the addition of the anti-VEGF antibody bevacizumab with trifluridine/tipiracil versus trifluridine/tipiracil alone in 492 patients.[31] This study demonstrated an improvement in both median OS (10.8 vs 7.5 months; HR, 0.61; 95% CI, 0.49-0.77; *P*<.001) and median PFS (5.6 vs 2.4 months; HR, 0.44; 95% CI, 0.36-0.54; *P*<.001) with the addition of bevacizumab. With the combination, grade 3 or higher AEs reported in patients included neutropenia (43.1%), anemia (6.1%), and hypertension (5.7%).

Fruquintinib in mCRC Without Targetable Mutations

Pivotal Trials of Fruquintinib in mCRC

The pivotal phase 3 FRESCO trial (416 patients) first evaluated fruquintinib in a population of patients from China who had mCRC treated with at least 2 prior lines of chemotherapy.[29] Compared with placebo, fruquintinib significantly prolonged median OS (9.30 vs 6.57 months; HR, 0.65; 95% CI, 0.51-0.83; *P*<.001) as well as median PFS (3.71 vs 1.84 months; HR, 0.26; 95% CI, 0.21-0.34; *P*<.001). The results of the FRESCO trial led to the approval of fruquintinib for the treatment of mCRC in China. Notably, at the time of patient enrollment into the FRESCO study, neither VEGF pathway inhibitors nor EGFR pathway inhibitors were considered standard of care treatment for mCRC in China. Thus, just 30% of patients had previously received a VEGF inhibitor, and only 14% had been treated with an EGFR inhibitor. Additionally, neither regorafenib nor trifluridine/tipiracil was available for treatment at that time; none of the patients enrolled in the study had any prior treatment with regorafenib or trifluridine/tipiracil. In FRESCO, dose interruptions owing to AEs occurred in 35.3% of patients in the fruquintinib arm (vs 10.2% in the placebo arm). Dose reductions owing to AEs were also more common with fruquintinib compared with placebo (24.1% vs 4.4%), as were discontinuations owing to AEs (15.1% vs 5.8%), most frequently because of proteinuria.

To better understand the efficacy and safety of fruquintinib in a group of patients reflective of current real-world populations, the pivotal FRESCO-2 trial was designed.[30] FRESCO-2 (691 patients) was an international, randomized, double-blind, placebo-controlled, phase 3 study that enrolled patients from across North America, Europe, Asia, and Australia. In particular, this study population was comprised of heavily pretreated patients (median of 4 prior lines of treatment for metastatic disease, and 73% had received more than 3 prior lines of therapy) with mCRC who were eligible only if they had received all standard treatments,

Table 4. Adverse Events Experienced by at Least 1 Patient in the Safety Population of the FRESCO-2 Study[30]

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.

including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if *RAS* wild-type). Indeed, most patients (96%) had received prior anti-VEGF therapy, and 39% had received prior anti-EGFR therapy. Additionally, patients were required to have either experienced disease progression on or been intolerant to trifluridine/tipiracil or regorafenib. At baseline, patients had received trifluridine/tipiracil (52%), regorafenib (8%), or both (39%). Median OS was significantly prolonged with fruquintinib compared with placebo (median OS, 7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; *P*<.0001), as was median PFS (3.7 vs 1.8 months; HR, 0.32; 95% CI, 0.27-0.39; *P*<.0001). In FRESCO-2, 47% of fruquintinib-treated patients experienced dose interruption owing to AEs (compared with 27% in the placebo arm). Dose reductions owing to AEs were also reported with a higher frequency in the fruquintinib arm compared with the placebo arm (24% vs 4%), primarily because of hand-foot syndrome (5%), hypertension (4%), and asthenia (4%). However, discontinuations owing to AEs occurred at a similar rate between the 2 treatment arms (20% in the fruquintinib arm and 21% in the placebo arm), most frequently because of asthenia (2%). Table 4 summarizes the most common AEs reported in the FRESCO-2 trial.

Fruquintinib Dosing and Administration in mCRC

Fruquintinib is administered for the first 21 days of each 28-day cycle at a recommended dose of 5 mg orally once daily, given at approximately the same time each day.[21] The recommended starting dose may be modified in the event of adverse reactions (Table 5). Dose modifications are recommended for specific AEs, including grade 3 hypertension, grade 2 hemorrhagic events, and grade 2 palmar-plantar erythrodysesthesia, as well as elevations of proteinuria (≥2 g in 24 hours) or signs of hepatotoxicity (ALT or AST >3 times the upper limit of normal). The first recommended dose reduction is to 4 mg once daily, and the second recommended dose reduction is to 3 mg once daily. In the event that even the 3-mg dose cannot be tolerated, fruquintinib should be permanently discontinued.

Table 5. Fruquintinib Dosing Summary per the Prescribing Information[21]

Category	Details
Recommended dose	5 mg once daily
Schedule	First 21 days of a 28-day cycle, continued until disease progression or until unacceptable toxicity
Administration	Oral capsule
Missed dose	Take a missed dose if less than 12 hours have passed since the missed scheduled dose; do not take 2 doses on the same day to make up for a missed dose
Vomiting after dose	Do not take an additional dose if vomiting occurs after taking dose, but continue with the next scheduled dose
Dose reductions for adverse reactions	First dose reduction to 4 mg orally once daily; second dose reduction to 3 mg orally once daily; permanently discontinue in patients unable to tolerate the 3 mg once daily dose
Available dosage forms and strengths	1 mg and 5 mg hard gelatin capsules

Grade 3 adverse reactions are generally managed by temporarily withholding fruquintinib, then resuming it at a reduced dose after resolution of the AE to grade 1 or lower.[21] Discontinuation of fruquintinib is recommended in patients with grade 4 adverse reactions, although resumption at a lower dose may be considered on an individual basis in the event of non–life-threatening toxicity.

Managing Potential Side Effects With Fruquintinib

The pivotal clinical trials of fruquintinib reported the toxicity profile of fruquintinib in patients with mCRC. Some of these AEs and their management are described in more detail in the fruquintinib prescribing information (Table 6).

Hypertension is a side effect common with fruquintinib; in clinical trials it was the most frequently reported AE with fruquintinib.[21,29,30] When initiating treatment with fruquintinib, a baseline blood pressure should be determined, followed by weekly monitoring during the first month, then monthly thereafter and as clinically indicated. Antihypertensive therapy is initiated or adjusted as needed for patients who experience elevated blood pressure. Grade 3 hypertension is managed with dose interruption and resumption at a reduced dose; grade 4 hypertension requires discontinuation of fruquintinib.

Hand-foot syndrome can also be a side effect of fruquintinib, and is typically managed by decreasing dose intensity, as either a dose delay or dose reduction.[21] To avoid patients having to decrease dose intensity, preventive measures may include loose-fitting clothes and shoes to reduce skin friction, avoiding heat, use of daily emollients and creams, and rapid treatment to skin erosions to prevent infection.

Diarrhea can also occur with fruquintinib.[21] It is important to engage in patient education and communication to keep track of its severity, and initiate treatment before it becomes severe. Over-the-counter treatments, such as loperamide, can be used to manage diarrhea, and rehydration with liquids that contain electrolytes and water is also essential.

Proteinuria was reported in 36% of fruquintinib-treated patients in the pooled safety population, including 2.5% grade 3 or higher events.[21] In patients who experience proteinuria of at least 2 g per 24 hours, fruquintinib should be withheld until the proteinuria is either fully resolved or dips below 1 g per 24 hours. Upon resolution, fruquintinib is then resumed at the next lower dose level. However, if the proteinuria does not recover to less than 1 g per 24 hours, or if the patient develops nephrotic syndrome, fruquintinib should be permanently discontinued.

Infections, including fatal infections, have been reported with fruquintinib.[21] In the pooled safety population of fruquintinib-treated patients, the most common infections reported 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%). Fruquintinib is withheld for grade 3 or 4 infections, or worsening infection of any grade, but it can be resumed at the same dose upon resolution of the infection.

Monitoring Response to Treatment

In most cases, imaging is the primary modality for monitoring treatment response in patients receiving third-line therapy for mCRC.[32] Imaging studies are typically performed with CT scans of the chest/abdomen/pelvis with contrast, although magnetic resonance imaging may be an alternative.[33] Frequent imaging, such as every 2 months, can help catch those patients who will experience rapid disease progression.

Careful monitoring of patient symptoms may also be useful when determining a patient's response to treatment.[34] This is especially the case for patients with a heavy tumor burden, in whom symptom palliation is an important treatment goal. In contrast, symptom palliation as an assessment of treatment response is less useful in patients with more

Table 6. Toxicity-Based Dose Reduction Criteria for Fruquintinib per the Prescribing Information[21]

Adverse reaction	Severity (according to NCI CTCAE v5.0)	Recommended dosage modification
Hypertension	Grade 3	• Withhold fruquintinib for grade 3 hypertension that persists despite optimal antihypertensive therapy • If hypertension fully resolves or recovers to grade 1, resume at the next lower dose level
	Grade 4	Permanently discontinue fruquintinib
Hemorrhagic events	Grade 2	• Withhold fruquintinib until bleeding fully resolves or recovers to grade 1 • Resume at the next lower dose level
	Grade 3/4	Permanently discontinue fruquintinib
Hepatotoxicity	ALT/AST >3×ULN[a] Or Bilirubin >1.5×ULN[a]	• Withhold fruquintinib and monitor AST, ALT, and total bilirubin until resolution to grade 1 or baseline • Resume at the next lower dose level
	ALT/AST >3×ULN with concurrent total bilirubin >2×ULN[b]	Permanently discontinue fruquintinib
	ALT/AST >20×ULN[a] Or Bilirubin >10×ULN[a]	Permanently discontinue fruquintinib
Proteinuria	≥2 g/24 h	• Withhold fruquintinib until proteinuria fully resolves or is <1 g/24 h • Upon recovery, resume at the next lower dose level • Permanently discontinue fruquintinib for nephrotic syndrome or if proteinuria does not recover to <1 g/24 h
Palmar-plantar erythrodysesthesia	Grade 2	• Withhold fruquintinib and initiate supportive treatment • If toxicity fully resolves or recovers to grade 1, resume at the same dose level
	Grade 3	• Withhold fruquintinib and initiate supportive treatment • If toxicity fully resolves or recovers to grade 1, resume at the next lower dose level

[a]Or baseline (instead of ULN) if baseline was abnormal. [b]In the absence of cholestasis or hemolysis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; g, grams; h, hours; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ULN, upper limit of normal.

indolent disease.

Likewise, serial tumor biomarkers such as carcinoembryonic antigen may be useful to detect tumor control.[10] Emerging biomarkers are under investigation; chief among these is circulating tumor, which may portend disease progression before radiological recurrence is observed.[35,36]

Bringing It All Together

For patients with mCRC, standard chemotherapy regimens can improve survival and disease control but can be associated with significant hematologic and nonhematologic toxicities. Nonchemotherapy options provide additional later-line treatment opportunities, particularly after progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens. For patients who wish to avoid IV therapy or frequent clinic visits, oral agents are often favored. Common oral agents used in this setting include fruquintinib, regorafenib, and trifluridine/tipiracil alone.

Trifluridine/tipiracil is a combination antimetabolite with a dual mechanism of action that causes DNA dysfunction and is often administered with bevacizumab, a monoclonal antibody that targets the VEGF-A ligand. Fruquintinib and regorafenib are oral kinase inhibitors with antiangiogenic activity that interfere with signaling pathways involved in tumor vascularization and growth. Regorafenib is a "promiscuous" oral multikinase inhibitor that targets angiogenic, stromal, and oncogenic pathways, simultaneously blocking multiple distinct receptor tyrosine kinases. Fruquintinib is a highly selective inhibitor of VEGFR-1,

VEGFR-2, and VEGFR-3, targeting angiogenic and lymphangiogenic signaling pathways that support tumor progression. In our patient, we chose fruquintinib given prior cytopenias and patient preference based on the FRESCO studies. The phase 3 FRESCO and FRESCO-2 studies demonstrated the efficacy and safety of fruquintinib in heavily pretreated patients with mCRC, many of whom had liver metastases, microsatellite-stable disease, and multiple prior lines of therapy. Fruquintinib significantly improved both OS and PFS compared with placebo.[29,30]

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