Case Study Series

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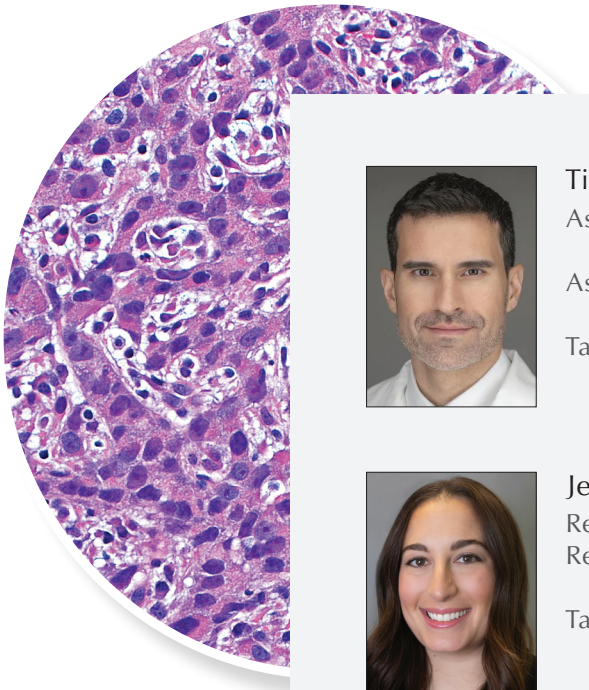
Translating FRESCO Clinical Trial Evidence Into Practice: Fruquintinib as Post–Standard Third-Line Therapy Followed by Trifluridine/Tipiracil in a Patient With mCRC Without Targetable Mutations



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Translating FRESCO Clinical Trial Evidence Into Practice: Fruquintinib as Post–Standard Third-Line Therapy Followed by Trifluridine/Tipiracil in a Patient With mCRC Without Targetable Mutations

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In the Clinic

JR is a 54-year-old male who was diagnosed with left-side transverse colon adenocarcinoma metastatic to the peritoneum and liver (Table 1). A next-generation sequencing panel showed a nontargetable *KRAS* A146T mutation, HER2-negative expression, and no other targetable gene alterations. The tumor had a low tumor mutational burden, and was microsatellite stable and mismatch repair intact.

This case was discussed in a gastrointestinal (GI) tumor board. The initial treatment was surgical resection of the primary tumor. The pathology report indicated a T4N2M1a. Circulating tumor DNA (ctDNA) after surgery was negative. Adjuvant FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) chemotherapy was initiated.

A follow-up surgery 5 months later showed a hernia sac positive for metastatic adenocarcinoma. Adjuvant FOLFOX was restarted; however, only 2 months later an abdominal magnetic resonance imaging (MRI) scan revealed new lesions in the right liver lobe concerning for metastasis. JR was switched to FOLFIRI (5-FU, leucovorin, and irinotecan) and after 8 cycles bevacizumab was added. While on FOLFIRI and bevacizumab, JR began experiencing significant myelotoxicity, evidenced by anemia, neutropenia, and thrombocytopenia.

About 3 months later JR was hospitalized for weakness and melena. At the time, an esophagogastroduodenoscopy was notable for esophageal varices without evidence of recent bleeding. Further evaluation by MRI showed enlargement of the spleen, which led to a diagnosis of portal hypertension likely secondary to previous chemotherapy exposure. The esophageal varices were attributed to portal hypertension. Based on this development, bevacizumab was discontinued. A subsequent MRI showed interval enlargement of multiple existing liver lesions as well as multiple new lesions consistent with progression of hepatic metastases confirmed by positron emission tomography (PET)/computed tomography (CT).

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

Credit: Ziad M. El-Zaatari/Science Source

Table 1. Patient Case Summary

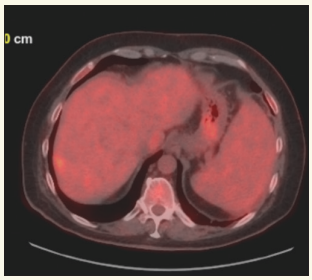
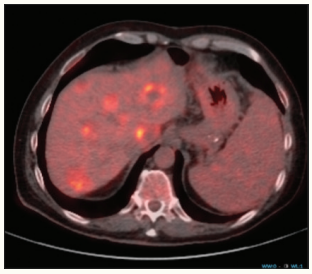
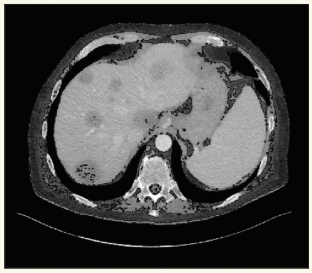
54-year-old male patient with transverse colon adenocarcinoma metastatic to peritoneum and liver; *KRAS* A146T, TMB-low, MSS, HER2-negative, MMR intact, UGT1A1 intermediate metabolizer, DPYD normal metabolizer	
01/2023	• Colonoscopy: fungating, infiltrative, and ulcerated obstructing mass in the transverse colon plus fungating and infiltrative partially obstructing mass in the sigmoid colon at about 40 cm from the anal verge **(moderately to poorly differentiated adenocarcinoma)** • CEA: 39.4 ng/mL • CT (abdomen and pelvis): focal segment of diffuse circumferential wall thickening within the mid transverse colon with multiple mildly enlarged pericolic lymph nodes and a few small hypoattenuating lesions within the right hepatic lobe • MRI (abdomen): 1.2 cm hypoenhancing lesion within segment 7 suspicious for metastasis
03/2023	• Robotic-assisted abdominal colectomy with ileorectal anastomosis, wedge resection of segments 5, 6, and 8 • Pathology consistent with pT4a N2 M1a with multiple primary sites (transverse and sigmoid colon), invading visceral peritoneum, 6 of 59 lymph nodes involved, liver metastasis in segments 5, 6, and 8, margins for segment 8 positive
04/2023	• Tumor-informed ctDNA test: negative (0.0 mean tumor molecules [MTM]/mL) • Port placement • **FOLFOX C1D1** • CEA 68.8 ng/mL
08/2023	• **FOLFOX C9D1 (5-FU continuous intravenous infusion only)**
09/2023	• Open liver wedge resection segment 6 and 7, liver ablation, cholecystectomy, ileostomy closure • Ileostomy: small bowel negative for malignancy • Hernia sac: **metastatic adenocarcinoma involving the fibromembranous tissue** • Liver wedge resection, segments 6 and 7: adenocarcinoma morphologically consistent with patient's history of colorectal adenocarcinoma
10/2023 to 12/2023	• GI tumor board recommendation: restarting systemic chemotherapy (as hernia sac positive for metastatic adenocarcinoma) • FOLFOX: C10D1 (no 5-FU/LV bolus); C14D1 (no oxaliplatin, 5-FU/LV bolus added) • MRI (abdomen): new lesions in the right lobe concerning for metastasis, several lesions in the most inferior portion of the right hepatic lobe may represent necrotic lesions
01/2024	• 5-FU/LV C15D1 • Disease progression in the liver, treatment switched to FOLFIRI
02/2024	• **FOLFIRI C1D1** • CEA 93.9 ng/mL
04/2024	• FOLFIRI C6D1
05/2024	• FOLFIRI C8D1; bevacizumab added
08/2024	• FOLFIRI C14D1 + bevacizumab C7 • Hospitalization for weakness and melena, EGD notable for esophageal varices without evidence of recent bleeding
09/2024	• FOLFIRI C15; bevacizumab discontinued • CEA 289 ng/mL
10/2024	• FOLFIRI C17 • CEA 497 ng/mL
11/2024	• MRI (abdomen): interval enlargement of multiple existing liver lesions as well as multiple new lesions consistent with progression of hepatic metastases

continued on page 4

Chemotherapy was stopped, and treatment with fruquintinib initiated. JR subsequently developed GI bleeding and was hospitalized for banding of 3 large varices. Fruquintinib was continued for about 6 months, until a PET/CT scan showed progression of metabolically active hepatic and peritoneal metastases, as well as multiple small pulmonary nodules. JR was then switched to trifluridine/tipiracil; he was unable to initiate it in combination with bevacizumab, as preferred in the National Comprehensive Cancer Network (NCCN) Guidelines, owing to his continued esophageal varices.

Imaging follow-up after 2 months showed enlarging

Table 1. Patient Case Summary *continued*

12/2024	• **PET/CT (12/01):** postsurgical changes in the right lower quadrant consistent with a large bowel resection and ostomy site formation but no evidence of recurrent FDG-avid primary bowel malignancy along the suture material; scattered throughout the right and left liver lobe are multiple low-attenuation lesions which have increased in metabolic activity and some of which have appeared since the prior PET/CT scan and consistent with progression of hepatic metastasis • Excision of abdominal mass, area behind the ostomy; pathology consistent with metastatic adenocarcinoma, *KRAS* mutated, MSS 
01/2025	• **Initiated fruquintinib** • Hospitalization for GI bleeding; procedure to complete banding of 3 large varices
04/2025	• CEA 301.4 ng/mL
06/2025	**PET/CT (06/29):** • Progression of metabolically active hepatic, peritoneal metastases • Multiple small pulmonary nodules, the larger nodules show increased metabolic activity above background levels, which is a change from 12/01/2024 
07/2025	• 07/08: CEA 406 ng/mL • **Initiated trifluridine/tipiracil;** unable to initiate bevacizumab owing to esophageal varices • 07/24: CEA 314.6 ng/mL
08/2025	• 08/06: CEA 521.5 ng/mL • 08/20: CEA 700.2 ng/mL
09/2025	• **CT (thorax/abdomen/pelvis [09/10]):** ▪ New left axillary and retrocrural adenopathy; enlarging pulmonary nodules suspicious for metastases ▪ Enlarging hepatic metastases; new/enlarging portacaval, periportal, and retroperitoneal adenopathy ▪ Slight increase in a minority of the peritoneal metastases (the majority unchanged); trace ascites; several points of small bowel and colonic contact by peritoneal tumor; no present bowel obstruction ▪ Similar right lower abdominal wall metastasis • **FOLFOX C1;** reduced oxaliplatin 20% with no 5-FU/LV bolus • CEA 1451.2 ng/mL 
10/2025	• EGD: large (>5 mm) esophageal varices with no bleeding and no stigmata of recent bleeding; completely eradicated; banded

5-FU, 5-fluorouracil; C, cycle; CEA, carcinoembryonic antigen; CT, computed tomography; D, day; EGD, esophagogastroduodenoscopy; FOLFIRI, 5-FU, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; LV, leucovorin; MMR, mismatch repair; MRI, magnetic resonance imaging; MSS, microsatellite stable; PET, positron emission tomography; TMB, tumor mutational burden.

pulmonary nodules suspicious for metastases, enlarging hepatic metastases with new and enlarging portacaval, periportal, and retroperitoneal adenopathy, and a slight increase in a minority of the peritoneal metastases. By this progression, JR had recovered from myelotoxicity and FOLFOX chemotherapy was started with a reduced oxaliplatin dosage and no 5-FU/leucovorin bolus.

mCRC Without Targetable Mutations

An estimated 154,270 new cases of colorectal cancer (CRC) are expected to be diagnosed in the United States in 2025, making it the fourth most commonly diagnosed cancer (after breast, prostate, and lung cancers).[1] Unfortunately, with a 5-year relative survival rate of 65.4%, it

disproportionately is the second deadliest cancer.

Metastasis is a common feature of CRC, with the liver being the most frequent target for disease spread.[2] Over 70% of patients with CRC experience metastatic disease (metastatic CRC [mCRC]), which can be found either at diagnosis (23% of patients) or as disease progresses over the course of treatment (up to 50% of patients).[1,3] Metastatic disease at diagnosis significantly impacts patient prognosis, reducing the 5-year relative survival rate to 16.2%.[1]

Traditionally, patients with mCRC progress through multiple lines of therapy, with each subsequent line associated with a declining progression-free survival (PFS) interval. A retrospective study of 120 patients with mCRC showed a PFS interval of 8.5 months (range, 4-23) following first-line treatment, 5 months (range, 4-7.5) after second-line treatment, and 3 months (range, 2-5.5) after third-line treatment.[4] As PFS has been established as an effective surrogate endpoint for overall survival (OS) in patients with mCRC, there is clearly a need to prolong the PFS duration.

The first- and second-line treatment of mCRC revolve around the use of the topoisomerase I inhibitor irinotecan and the platinum agent oxaliplatin as the basis of the FOLFOX and FOLFIRI combination chemotherapy regimens. Similar outcomes in PFS, time to progression, and OS were demonstrated between the 2 regimens in the GOIM (Gruppo Oncologico dell'Italia Meridionale) and GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) studies. Subsequently, the 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) regimen was found to further prolong PFS and OS but at the cost of increased toxicity. Capecitabine has also been an important addition in the initial treatment of mCRC associated with improved efficacy outcomes compared with 5-FU plus leucovorin.[5]

A critical improvement in the first- and second-line treatment of mCRC came with the introduction of agents that inhibited either the vascular endothelial growth factor (VEGF) pathway (namely, bevacizumab, aflibercept, or ramucirumab) or the epidermal growth factor receptor (EGFR) pathway (for example, cetuximab or panitumumab). The pivotal trials evaluating their addition to chemotherapy demonstrated significant improvements in OS and PFS in the first-line setting. In particular, the anti-EGFR agents were the first to show specificity according to *KRAS* mutation status, as their efficacy is primarily limited to mCRC tumors harboring wild-type *KRAS*.[5,6]

Currently there are several options for patients after they have progressed through first- and second-line therapy. Over the past decade, multiple targeted agents have been approved for mCRC tumors harboring actionable mutations. In addition, immune checkpoint inhibitor therapy has proven clinically impactful in mCRC tumors that are characterized as microsatellite instability-high (MSI-H), mismatch repair deficient, or harboring *POLE*/*POLD1* polymerase mutations.[7] However, the majority of mCRC tumors fall into neither the category of having a targetable mutation nor of having characteristics qualifying for immune checkpoint inhibitor therapy.[8] Therefore most patients with mCRC do not benefit from these treatments, and require other interventions in the third-line and later setting.

Post–Standard Therapy Third-Line Options in mCRC Without Targetable Mutations

Treatment Options and Their Place in Therapy

As of late 2025, there are 3 agents approved by the US Food and Drug Administration in the third-line setting for patients with mCRC without targetable mutations who have received standard therapy: regorafenib, trifluridine/tipiracil, and fruquintinib (Figure 1).[9-11] For trifluridine/tipiracil, this indication applies both as a monotherapy and in combination with bevacizumab.[10] All of these agents are 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.[9-11]

Two of these agents, regorafenib and fruquintinib, are tyrosine kinase inhibitors (TKIs) of the vascular endothelial growth factor receptors (VEGFR), highlighting the importance of this pathway in mCRC and related tumor angiogenesis.[12] The VEGF molecule binding to one of its target tyrosine kinase receptors (VEGFR-1, VEGFR-2, or VEGFR-3) results in receptor activation and subsequent phosphorylation of its kinase domain. This results in downstream activation of intracellular signaling pathways that culminate in angiogenesis (VEGFR-1- and VEGFR-2-triggered pathways) and lymphangiogenesis (VEGFR-3-triggered pathways).[13]

Trifluridine/tipiracil is a combination of 2 drugs—a thymidine-based nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil).[14] By inhibiting thymidine phosphorylase, tipiracil inhibits the metabolism of trifluridine, resulting in increased trifluridine exposure. Trifluridine is incorporated into DNA, interfering with its synthesis and resulting in decreased cell proliferation.

Table 2 summarizes the pivotal trials supporting the indications for these agents in mCRC. All of these trials are similarly designed phase 3 trials that recruited

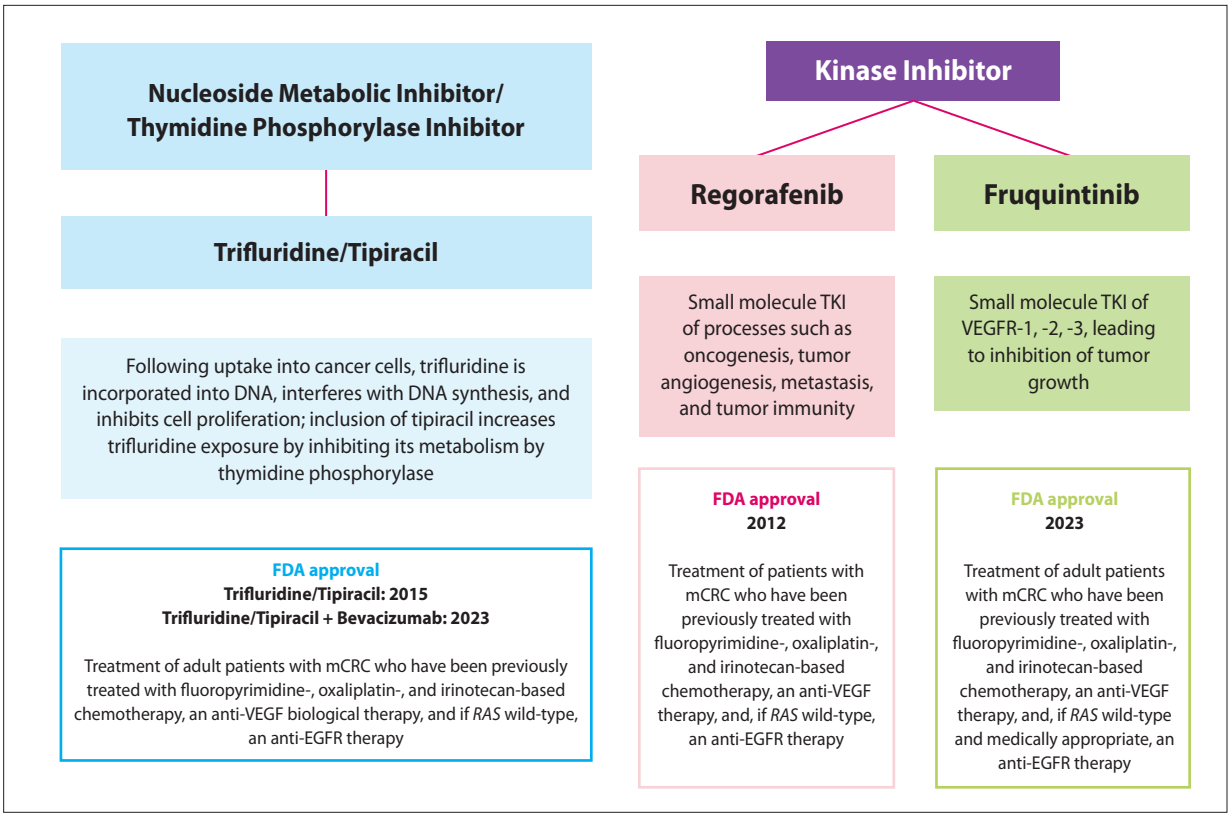


Figure 1. Post–standard therapy agents used in the third line for the treatment of mCRC with no targetable mutations.[9-11]

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

fairly large populations of patients with treatment-refractory mCRC.[15-21] The NCCN Guidelines recommend each of these 4 regimens as 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.[7] The NCCN Guidelines further state that, for trifluridine/tipiracil specifically, its combination with bevacizumab is preferred over trifluridine/tipiracil alone.

Regorafenib

The phase 3 CORRECT and CONCUR studies were the pivotal trials leading to regorafenib's approval in 2012.[15,16] CORRECT was an international trial that included patients from North America, Europe, Asia, and Australia; thus the approved standard therapies that patients received in the first- and second-line varied but had 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).[15] CONCUR was conducted to confirm the efficacy and safety of regorafenib in a large population of Asian patients with refractory mCRC located throughout China, Hong Kong, South Korea, Taiwan, and Vietnam. Unlike CORRECT, the CONCUR study permitted inclusion of patients who had not been treated with a biologic agent, as these agents were not widely available in some Asian countries at the time of the trial.[16] Overall, 40% of the CONCUR study population had not previously received any targeted biologic agent.

Both studies showed a significant improvement in median OS and median PFS with regorafenib vs placebo.[15,16] The most frequently reported grade 3 or higher adverse events (AEs) in the regorafenib arm were hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash/desquamation in the CORRECT study; and HFSR, hypertension, elevated alanine aminotransferase, and elevated aspartate aminotransferase in the CONCUR study.

Trifluridine/Tipiracil

The RECOURSE and TERRA trials were the phase 3

pivotal trials that resulted in the approval of trifluridine/tipiracil in 2015 for mCRC.[17,18] TERRA was a confirmatory study designed in a similar manner as the RECOURSE study to evaluate trifluridine/tipiracil in an Asian population.[18] Median OS and median PFS were significantly improved in the trifluridine/tipiracil arm compared with placebo in both trials.[17,18] The most common grade 3 or higher AEs in the trifluridine/tipiracil arm were neutropenia, leukopenia, anemia, and thrombocytopenia in RECOURSE; and neutropenia, leukopenia, anemia, and lymphopenia in TERRA.

Trifluridine/tipiracil plus bevacizumab approval in 2023 was based on the SUNLIGHT trial.[19] This study was designed to determine if the response rates achieved with trifluridine/tipiracil could be bolstered with a strategy of continuous inhibition of angiogenesis with bevacizumab. In SUNLIGHT, trifluridine/tipiracil plus bevacizumab was compared with trifluridine/tipiracil. Both the median OS and median PFS were significantly improved with the combination. The most frequent grade 3 or higher AEs in the combination arm were neutropenia, anemia, and hypertension.

Fruquintinib

The approval of fruquintinib in 2023 was based on the results of 2 clinical trials: FRESCO and FRESCO-2.[20,21] Conducted in China, FRESCO was a phase 3 study in patients with mCRC who had received at least 2 prior lines of chemotherapy.[20] Median OS and median PFS were significantly improved with fruquintinib vs placebo. The most frequent grade 3 or higher AEs were hypertension and HFSR.

Based on these results, fruquintinib gained approval for mCRC in China. However, it is important to note that when the FRESCO study was conducted, neither VEGF pathway inhibitors nor EGFR pathway inhibitors were routinely used as part of the standard of care treatment for mCRC in China; additionally, neither regorafenib nor trifluridine/tipiracil was available. This is reflected in the baseline characteristics of the FRESCO patient population, as only a minority of patients had previously received a VEGF inhibitor (30%) or EGFR inhibitor (14%) prior to receiving fruquintinib, and no patient had any prior treatment with regorafenib nor trifluridine/tipiracil.

FRESCO-2 was conducted in 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] Median OS and median PFS were significantly prolonged with fruquintinib vs placebo. The most frequent grade 3 or higher AEs were hypertension, asthenia, and HFS.

Fruquintinib and Trifluridine/Tipiracil Combination Being Investigated

Although the SUNLIGHT trial demonstrated that trifluridine/tipiracil plus bevacizumab is associated with improved outcomes over trifluridine/tipiracil alone, the benefit diminishes in patients previously exposed to bevacizumab. Thus different combinations have been explored. At the 2025 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, efficacy and safety data from a single-arm, open-label, phase 2 trial evaluating the combination of fruquintinib and trifluridine/tipiracil as a third-line treatment for patients with mCRC revealed a median PFS of 6.33 months and median OS of 18.4 months.[22] Although not yet practice-changing, this combination may expand future options in biomarker-negative refractory mCRC.

Goal of Third-Line Post–Standard Therapy

Most patients in the third-line setting have been receiving combination chemotherapy regimens for the better part of 2 to 3 years when their treatment was adjusted based on tumor response as observed with routine imaging. In the third-line setting, patients have reached a point where their tumor is unlikely to shrink. The goal in the third-line setting therefore is tumor stabilization and prolonging life expectancy with a focus on quality of life. Hence it is important to consider agents that give patients a break from toxicities they have experienced in the first- and second-line settings.[23]

Patients must be educated about this, as it can be

Patient Subgroups Likely to Benefit From Fruquintinib in the Third-Line Setting

Fruquintinib may be particularly advantageous in patients for whom trifluridine/tipiracil plus bevacizumab poses heightened risk. This includes individuals with bleeding tendencies or vascular comorbidities, where bevacizumab is contraindicated. Patients with prior chemotherapy-related myelotoxicity also represent an important subgroup, as fruquintinib offers disease control without further marrow suppression. Finally, fruquintinib provides an all-oral option, appealing to patients seeking to avoid infusion-based therapies.

Table 2. Post–Standard Therapy Agents Used in the Third Line for the Treatment of mCRC With No Targetable Mutations: Summary of Pivotal Trials[15-21]

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

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

extremely frustrating for them to undergo treatment but not "see" any results in the form of tumor shrinkage. In our clinic, such discussions are initiated in the months leading up to the third-line treatment, typically when patients are transitioned to second-line therapy where response rates are modest.

Mechanism of Action and Other Considerations When Sequencing Agents

There is a marked absence of head-to-head comparative studies evaluating third-line therapeutic options post–standard therapy. Thus each agent may be considered appropriate depending on the individual patient. There remains an open question surrounding the optimal sequencing of these agents which is essential when considering that as outcomes have improved over the past decades, an increasing number of patients have become eligible for treatment in the later-line settings.[24] There is no specific guidance in the NCCN Guidelines regarding the sequencing of these agents in the third-line and later treatment of mCRC. The NCCN Guidelines state that fruquintinib can be administered before or after trifluridine/tipiracil or regorafenib, with no data available to inform the best order of these therapies.[7]

As patients progress through lines of treatment for mCRC, the burden of accumulating AEs can become increasingly pronounced. Myelosuppression is common with chemotherapy administered during the first- and second-line setting. Residual myelosuppression needs to be considered as the patient moves into the third line, especially as trifluridine/tipiracil is associated with hematologic toxicities including neutropenia, anemia,

In the Clinic . . .

In selecting third-line therapy, JR's esophageal varices were a central consideration, as these had arisen from portal hypertension secondary to prior oxaliplatin exposure. The associated bleeding risk precluded the use of bevacizumab, thereby delaying initiation of trifluridine/tipiracil, which is preferentially administered in combination with bevacizumab. Compounding this, the patient had experienced significant myelotoxicity with earlier chemotherapy, making a non–myelosuppressive option desirable. Fruquintinib was therefore chosen. Although regorafenib would have been a reasonable alternative, fruquintinib was favored based on clinical experience suggesting superior tolerability, likely attributable to its more selective VEGFR inhibition.

This sequencing strategy achieved its primary objective of maintaining quality of life while prolonging life in the third-line setting. Fruquintinib provided disease control with only mild GI toxicity and manageable fatigue, allowing the patient a period of hematologic recovery. This interval facilitated transition to fourth-line trifluridine/tipiracil monotherapy. Importantly, the restoration of marrow reserve has enabled consideration of splenic artery embolization to further optimize hematologic parameters, with the ultimate goal of reintroducing bevacizumab.

and thrombocytopenia. In contrast, both regorafenib and fruquintinib are associated with low rates of hematologic AEs.

Fruquintinib is a nonchemotherapy TKI that inhibits all 3 VEGFRs, resulting in reduced tumor growth and progression as well as inhibition of lymphangiogenesis. Unlike other VEGFR inhibitors (including sunitinib, sorafenib, regorafenib, and pazopanib), fruquintinib demonstrates limited off-target kinase activity. This allows fruquintinib to be administered at doses that result in sustained target inhibition.[13,25] In contrast, regorafenib is a multitargeted TKI that inhibits VEGFR-1, -2, and -3. In addition, in preclinical studies, regorafenib has been shown 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 clinically relevant concentrations.[9]

This difference is important, as TKIs with a broad activity against multiple receptors can be associated with more toxicities, which are also varyingly manageable.[26] For instance, GI toxicities such as diarrhea or nausea can be easily managed with medications. Hand-foot syndrome, a common issue particularly with regorafenib, can be managed prophylactically with topical urea cream; diclofenac gel can help relieve associated pain. Fatigue, however, is trickier and is generally managed with dose modifications.

Closely monitoring the patient remains an important measure to manage nonhematologic toxicities, minimize their impact on quality of life, and maximize the clinical benefit of treatment.[27]

Evaluating Treatment Response

Generally, imaging is the primary mode for evaluation of treatment response, even in a setting where disease stabilization is expected. For the first few months, imaging scans may be performed frequently (ie, every 2 months instead of every 3 months) as patients are at a high risk of disease progression. This schedule is generally effective for patients who are minimally symptomatic at baseline. Imaging studies typically include CT scans of the chest/abdomen/pelvis with contrast; MRI may also be used.[28]

Serial tumor biomarkers, including carcinoembryonic antigen and carbohydrate antigen 19-9, assessed every 4 weeks, can provide valuable insight into signs of disease progression. Emerging biomarkers, such as ctDNA, are being validated for their potential to identify disease progression even before identification of radiological recurrence.[29,30]

Tracking patient symptoms can also be a useful strategy for monitoring disease progression as well as treatment-related toxicities. For example, the specific symptoms being palliated can be assessed to determine if symptom palliation is indeed being achieved. However, symptom palliation alone is not always reflective of treatment response, particularly in cases of indolent disease.[31]

Managing Potential Side Effects

Hand-Foot Syndrome

Once it occurs, management of hand-foot syndrome, a notable side effect of the TKIs regorafenib and fruquintinib, generally involves decreasing dose intensity, either as a dose delay or dose reduction.[32] Thus prevention is an important means to avoid reductions in dose intensity. Preventive measures may include reducing skin friction by wearing loose-fitting clothes and shoes, heat avoidance, incorporation of emollients and creams in daily routines, and rapid attention to skin erosions that may become infected.

Hypertension

Hypertension has been identified as a class effect of VEGF inhibitors, including fruquintinib and regorafenib, and is

manageable with appropriate monitoring and antihypertensive therapy.[33] Treatment initiation with fruquintinib requires controlled baseline blood pressure followed by weekly monitoring during the first month, then monthly thereafter and as clinically indicated.[11] When hypertension does occur, antihypertensive therapy should be either initiated or adjusted as needed.

Diarrhea

GI effects, particularly diarrhea, can also occur with TKIs such as fruquintinib and regorafenib.[34] Patient education and communication are essential to optimize management, and treatment should be given before it advances in severity. Diarrhea can be treated with an over-the-counter remedy such as loperamide, as well as rehydration with liquids that contain electrolytes and water, but this should be done with monitoring to ensure symptoms do not become severe.

Fatigue

Fatigue can be a common and difficult-to-treat symptom in the third-line and later treatment setting for mCRC. Frequent check-ins assessing the patient's fatigue levels can help identify issues, and management includes a dose hold followed by a dose reduction in patients with significant fatigue.

Dose Modification Strategies to Manage Adverse Events

AEs associated with regorafenib tend to appear early, often within the first 2 weeks of therapy. In many cases, this leads to early dose modifications, meaning that patients often do not achieve the prolonged dosing of regorafenib needed, given its action as a cytostatic agent. An alternative regorafenib dose-escalation strategy, which was tested in the ReDOS study, has largely influenced how regorafenib is currently administered in the clinic.[35,36]

The recommended starting dose of fruquitinib is 5 mg orally once daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.[11] Dose modifications are recommended for certain AEs, including grade 3 hypertension, grade 2 hemorrhagic events, grade 2 palmar-plantar erythrodysesthesia, as well as elevations of proteinuria (≥2 g in 24 hours) or signs of hepatotoxicity (alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal). In general, it is recommended that the first dose reduction is to 4 mg, and the second dose reduction is to 3 mg. Quickly transitioning a patient to these new doses can be difficult, as this requires insurance approval of the alternative 1 mg per capsule formulation. One strategy to mitigate this challenge is to use an alternative dosing strategy—for example, weekends off or a 2 days on/1 day off schedule.

Back to the Clinic

Let us reconsider JR's case in the context of the choice of third-line and later treatments. Like many patients, JR was diagnosed with CRC that had already metastasized to the abdominal lymph nodes and liver. After surgery, JR received standard first-line therapy with FOLFOX, that was switched to FOLFIRI in the second line following disease progression. JR's mCRC lacked both targetable mutations as well as genomic alterations such as MSI-H or tumor mutational burden-high, meaning that in the third line he was not a candidate for targeted agents or immune checkpoint inhibitor therapy, respectively.

The cytotoxic regimens that JR received had taken their toll, and by the time he approached his transition to third-line therapy, he had developed esophageal varices secondary to portal hypertension as well as significant myelotoxicity. For these reasons, the possibility of switching to a nonchemotherapy treatment option for this third-line therapy were discussed. JR was eager to experience a reprieve from both his rigorous infusion schedule and the side effects he had developed. However, it took some time for his mindset to shift from his regular routine of follow-up imaging scans, hoping for a reduction in his tumor burden. JR was educated on the idea of achieving disease stability, and how this plus a lower burden of toxicity could not just prolong his life but do so while maintaining his quality of life.

Owing to both the esophageal varices as well as the prolonged myelotoxicity, it was decided not to immediately switch JR to third-line trifluridine/tipiracil. The esophageal varices precluded its combination with bevacizumab, and it was prudent to allow his blood cell counts to recover before initiating trifluridine/tipiracil, which is associated with anemia, neutropenia, and thrombocytopenia. Regorafenib was also considered, but its toxicity profile, reflective of its broad, multikinase inhibition, can be difficult for patients. Hence, the more selective TKI fruquitinib was selected for JR's third-line treatment.

JR experienced disease stabilization for about 6 months; during that time he did not have significant AEs and also recovered his blood cell count. His 6-month period of disease stability was nearly twice that reported in the FRESCO-2 study.[21] When his tumor ultimately progressed, JR was able to switch to another chemotherapy regimen, trifluridine/tipiracil, as his fourth-line treatment. However, his esophageal varices precluded the addition of bevacizumab, and 2 months later he showed disease progression (reflective of the 2-month median PFS reported in both the RECOURSE and TERRA studies).[17,18] Importantly, with the nearly 8 months that JR had been able to continue with disease stability in the absence of cytotoxic chemotherapy, his overall condition

improved to the point that he was able to tolerate more aggressive therapy again. As a result, JR has begun fifth-line treatment with a dose-reduced FOLFOX regimen.

Disclosures

Dr Biachi has served on a speaker's bureau, as a consultant, or in an advisory role for Bayer, Moderna, AstraZeneca, and Takeda; participated in travel and conferences for Ipsen and Moderna; and conducted research for Ipsen and Astellas.

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