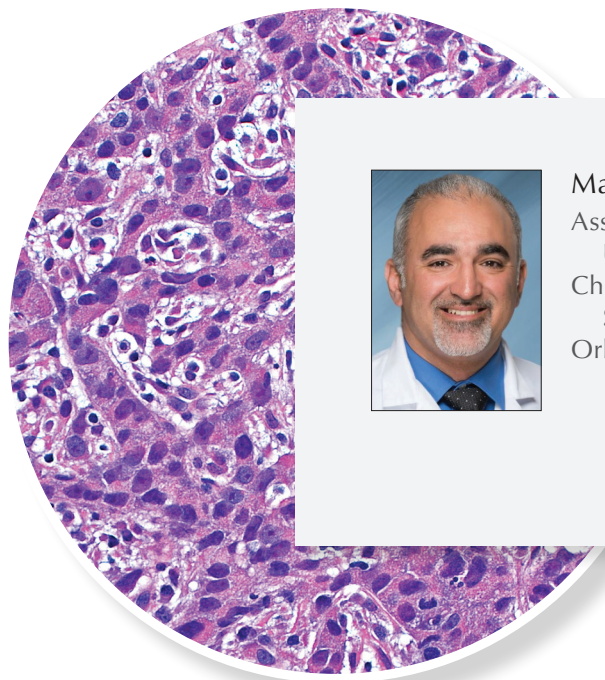


Case Study Series

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Fruquintinib as Post-Standard Third-Line Therapy in a Patient With mCRC Without Targetable Mutations: A Real-World Application of FRESCO Trial Principles



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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 Erythrodysesthesia (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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About the Patient

SB is a 72-year-old male with a prior history of pT2N2 adenocarcinoma of the cecum that was initially diagnosed in 2014 (Figure 1). At the time of initial diagnosis, he underwent surgical resection followed by adjuvant chemotherapy with capecitabine and oxaliplatin (CAPEOX). Since then, he has undergone chest/abdomen/pelvis computed tomography (CT) imaging every 6 months.

Approximately 5 years later, in September 2019, liver lesions were noted in the follow-up CT scan. This imaging result was accompanied by noticeable weight loss and fatigue, which SB reported. A biopsy was performed, and in October 2019, he was diagnosed with stage IV metastatic rectal adenocarcinoma with hepatic metastases. Molecular profiling of the biopsy specimen revealed a *KRAS* mutation but no targetable genetic alterations.

First-line systemic therapy for metastatic disease consisted of CAPEOX in combination with bevacizumab. This first-line regimen was administered every 3 weeks from May 2020 through November 2020. SB rapidly achieved a favorable clinical and radiographic response. SB experienced grade 2 diarrhea that was effectively controlled with over-the-counter loperamide. The patient was maintained on capecitabine and bevacizumab until December 2024.

Surveillance imaging was continued every 3 months over the course of treatment. In December 2024, the CT scan revealed radiographic progression with new lesions on the liver as well as new involvement in the lung. An assessment of SB's overall health determined he had an Eastern

Cooperative Oncology Group (ECOG) performance status of 1. In January 2025, second-line treatment was initiated with FOLFIRI (5-fluorouracil [5-FU]/leucovorin plus irinotecan). SB experienced an increase in diarrhea, for which loperamide was again recommended. He also developed grade 3 neutropenia that was monitored and addressed with dose adjustments.

During SB's second-line treatment, his oncologist began to discuss with him his options for treatment after he inevitably progressed on second-line therapy. In these conversations, the oncologist began educating SB on the shifting goals of treatment as he progressed beyond second-line treatment. He also provided SB with background on the use of non-chemotherapy treatments to allow his body a chance to recover from the effects of multiple years of chemotherapy.

Second-line FOLFIRI was continued until June 2025, when further radiographic progression was documented. In a conversation with SB, his oncologist described the non-chemotherapy options available to SB, including fruquintinib, regorafenib, and trifluridine/tipiracil (either alone or in combination with bevacizumab). After a discussion with SB that included shared decision-making, third-line treatment with fruquintinib was initiated in July 2025.

SB achieved a rapid response to fruquintinib, particularly with respect to the hepatic lesions that persisted after FOLFIRI treatment. Overall, he has tolerated fruquintinib well, though he developed grade 1 hypertension in the first few weeks of treatment, for which anti-hypertensive therapy was begun. The selection of this treatment strategy was based on the patient's prior sustained response to bevacizumab, as

On the Cover

Light micrograph of a poorly differentiated colon adenocarcinoma.

Credit: Ziad M. El-Zaatari/Science Source

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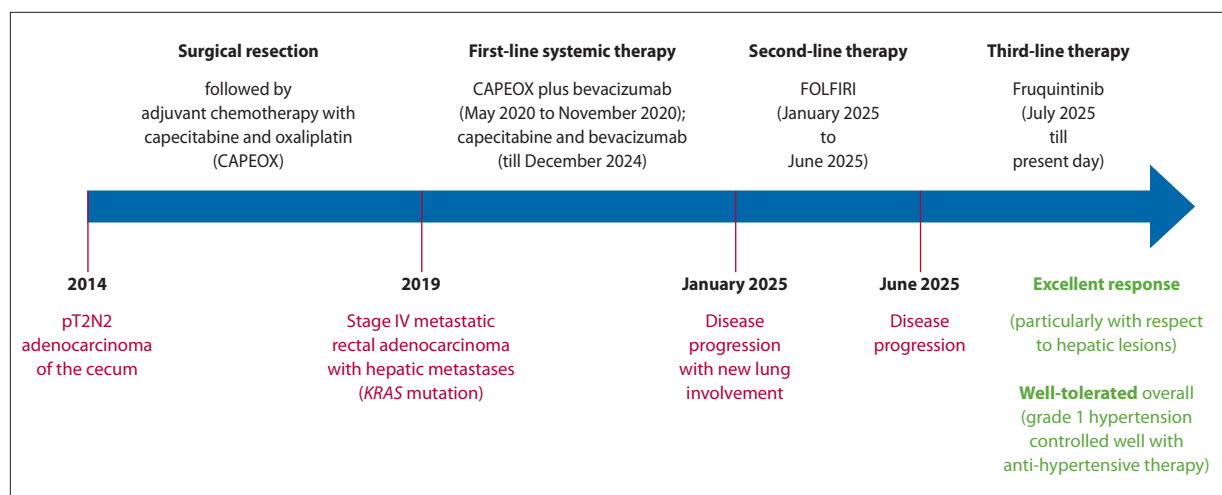


Figure 1. Patient case timeline.

well as the non-cytotoxic profile of fruquintinib, making it a suitable and effective regimen in this setting. SB remains on fruquintinib.

Overview of mCRC

Disease Burden

An estimated 158,850 new cases of colorectal cancer (CRC) are expected to be diagnosed in the United States in 2026, with an expected mortality of 55,230 people.¹ Remarkably, adults under the age of 65 years now account for nearly half (45%) of new CRC diagnoses, nearly double the proportion in this age group in 1995 (when it accounted for 27% of new CRC diagnoses).¹ While the 5-year relative survival rate has improved over that same period, it remains just 65% (estimated for 2015 to 2021).¹

Ultimately, most patients develop metastatic disease (metastatic CRC [mCRC]), either as disease progression after primary treatment (up to 50%) or presenting at diagnosis (approximately 23%).^{2,3} The liver is the most common site for metastasis, followed by the thorax.⁴ Metastatic disease has a significant impact on patient outcomes, as the 5-year relative survival dips to just 16.9% in patients with distant metastases.² Partly explaining this reduced survival is the rapidly declining length of progression-free survival (PFS) that patients experience as they progress through lines of treatment. As one retrospective single-center study showed, PFS decreases from 8.5 months (range, 4-23) with first-line therapy to 5 months (range, 4-7.5) in the second line, and an even shorter 3 months (range, 2-5.5) in the third line.⁵

Prolonging PFS with each line of therapy appears to be an important goal in mCRC treatment, where PFS can serve as a surrogate endpoint for overall survival (OS).⁵ This must be balanced against maintaining quality of life (QOL) of the patient, an increasingly recognized outcome that has

been correlated with improvements in survival in mCRC.⁶

Therapeutic Options in mCRC

The treatment of mCRC has advanced considerably over the past several years.

As early as the 1950s, 5-FU was demonstrated as initially effective in CRC.⁷ Addition of the reduced folate leucovorin appeared to improve outcomes,⁷ which was confirmed with the publication of a 2004 meta-analysis showing this combination improved tumor response rates with a modest benefit in OS.⁸

The topoisomerase I inhibitor irinotecan and the platinum agent oxaliplatin were added, forming the combination chemotherapy regimens FOLFOX (5-FU/leucovorin plus oxaliplatin) and FOLFIRI that are still used today.⁷ Two studies, reported from the GOIM (Gruppo Oncologico Dell'Italia Meridionale) and GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) groups, demonstrated similar benefits in patient outcomes between the 2 regimens, including PFS, OS, and time to progression (TTP).⁷ The combination of all of these agents into the FOLFOXIRI (5-FU/leucovorin, oxaliplatin, and irinotecan) regimen was shown to improve efficacy but at the cost of increased toxicity.⁷ The oral 5-FU prodrug capecitabine was also added to the treatment armamentarium, as it showed improved efficacy outcomes compared with 5-FU/leucovorin.⁷

In a major leap forward, agents that inhibited either the vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) pathways were found to significantly improve survival outcomes when added into the first-line setting.⁷ First, the addition of the anti-VEGF antibody bevacizumab (and later, aflibercept and the VEGF receptor inhibitor ramucirumab) to chemotherapy achieved significantly increased OS and PFS compared with che-

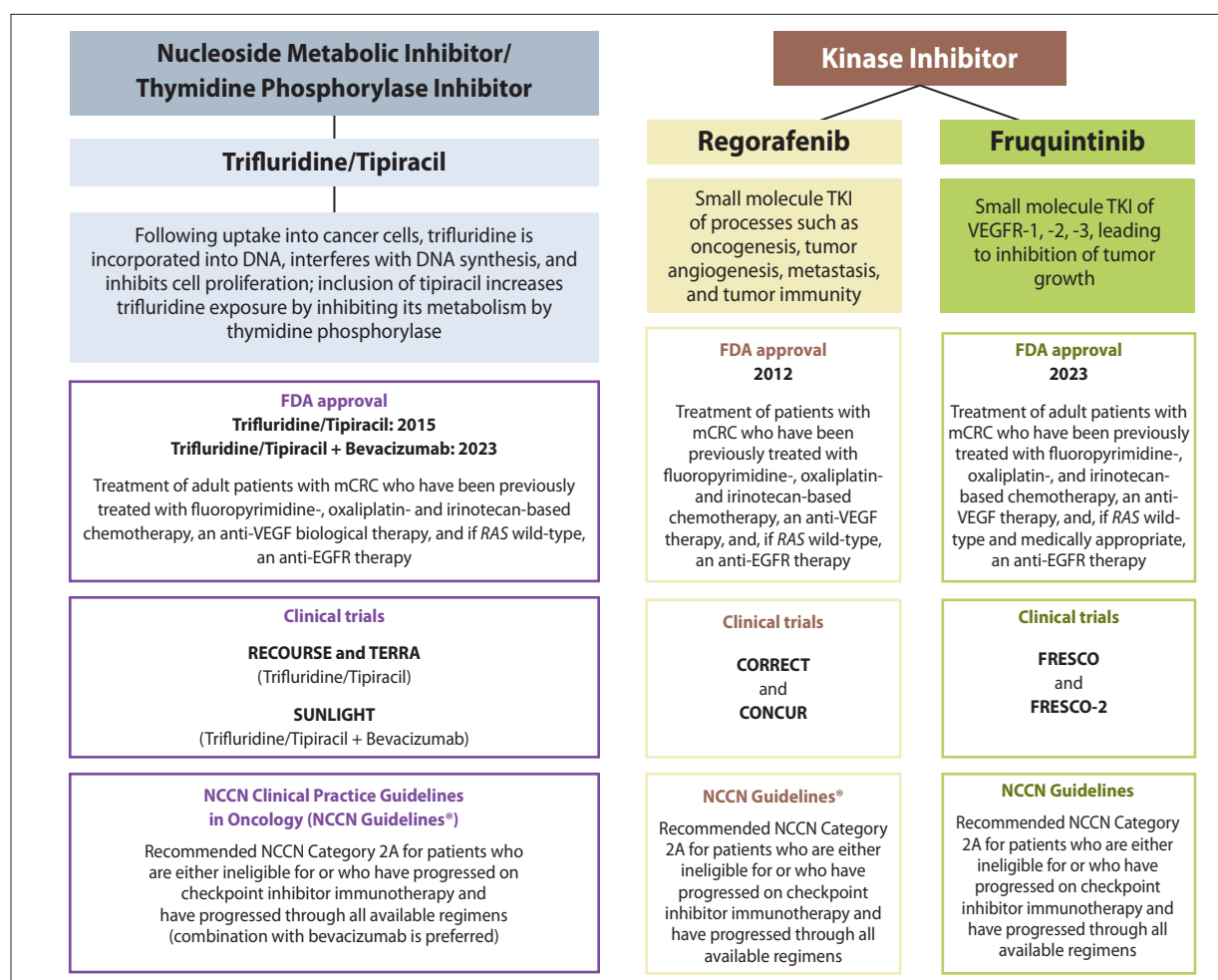


Figure 2. Post-standard therapy agents used in the third line for the treatment of mCRC with no targetable mutations.^{11,14-16}

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.

monotherapy alone.^{7,9} Prolongation of OS and PFS was also achieved with the addition of the anti-EGFR antibodies cetuximab or panitumumab.^{7,9} Pivotal studies demonstrated that the efficacy attributed to the addition of the anti-EGFR agents was primarily limited to mCRC harboring wild-type *KRAS*, providing molecular guidance on therapeutic selection.⁷

A subset of patients with mCRC have tumors harboring actionable mutations. For these patients, multiple targeted agents have now been approved over the past decade that target these actionable mutations.¹⁰ Further, stratifying mCRC tumors as microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR), and *POLE*/*POLD1* polymerase mutations has now opened up the use of immune checkpoint inhibitor therapy for these patients.¹¹

However, the majority of patients with mCRC have tumors that do not harbor actionable mutations or dMMR status. For these patients, approved targeted agents and

immune checkpoint inhibitors are not beneficial, and therefore, alternative treatments are needed for disease progression following standard of care treatment.¹²

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

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

By the time patients reach the third-line treatment setting, most have been treated with combination chemotherapy regimens for at least 2 to 3 years. These treatments are given with the goal of prolonging OS and PFS. However, in the third-line, goals of treatment shift such that prolonging survival remains a focus but is balanced against maintaining patient QOL.¹³ These goals and expectations for treatment must be proactively discussed with patients, so that they understand the shift from a goal of tumor

shrinkage to tumor stabilization.

In the United States, 3 agents are approved by the US Food and Drug Administration (FDA) in the setting of third-line post-standard therapy for patients with mCRC without targetable mutations: regorafenib, trifluridine/tipiracil (administered either with or without bevacizumab), and fruquintinib (Figure 2). All 3 agents are indicated only after patients have exhausted standard treatments in the first- and second-line, which must have included fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy.¹⁴⁻¹⁶

NCCN Guidelines

All 4 FDA-approved regimens (regorafenib, trifluridine/tipiracil alone, trifluridine/tipiracil plus bevacizumab, and fruquintinib) are recommended by the NCCN Guidelines for patients who are either ineligible for or who have progressed on checkpoint inhibitor immunotherapy and have progressed through all available regimens.¹¹ All 4 regimens are included with a NCCN Category 2A recommendation, with the guidelines noting that the combination of trifluridine/tipiracil with bevacizumab is preferred over trifluridine/tipiracil alone.¹¹ Fruquintinib can be given before or after trifluridine/tipiracil (with or without bevacizumab) or regorafenib; there are no data to inform the best order of these therapies. *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.*

Pivotal Trials

The pivotal trials supporting the FDA approval of these 4 regimens were similarly designed phase 3, placebo-controlled trials (with the exception of the combination of trifluridine/tipiracil with bevacizumab, which was compared with trifluridine/tipiracil alone) in large populations of patients with treatment-refractory mCRC.¹⁷⁻²³ All of these trials demonstrated prolonged survival with the third-line agent compared with placebo, with primary endpoint median OS ranging from 6.4 months with regorafenib to 9.3 months with fruquintinib, and the secondary endpoint median PFS ranging from 1.9 months with regorafenib to 3.7 months with fruquintinib.¹⁷⁻²³

The phase 3 CORRECT (N=760) and CONCUR (N=204) trials evaluated regorafenib as third-line therapy in mCRC.^{17,18} Median OS in the CORRECT trial was prolonged with regorafenib compared with placebo (6.4 vs 5.0 months, respectively; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; $P=.0052$), as was median PFS (1.9 vs 1.7 months, respectively; HR, 0.49; 95% CI, 0.42-0.58; $P<.0001$).¹⁷ Regorafenib was also found to be significantly superior to placebo in the CONCUR trial, demonstrating a median OS of 8.8 vs 6.3 months (HR, 0.55; 95% CI,

0.40-0.77; $P=.00016$), and a median PFS of 3.2 vs 1.7 months (HR, 0.31; 95% CI, 0.22-0.44; $P<.0001$).¹⁸ In the regorafenib arm of the CORRECT trial, the most common ($\geq 5\%$ of patients) grade 3 or higher adverse events (AEs) were hand-foot skin reaction (HFSR; 17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash/desquamation (6%).¹⁷ In the regorafenib arm of CONCUR, the most common ($\geq 5\%$ of patients) grade 3 or higher AEs reported were HFSR (16%), hypertension (11%), elevated alanine aminotransferase (ALT; 7%), and elevated aspartate aminotransferase (AST; 6%).¹⁸

The phase 3 RECURSE (N=800) and TERRA (N=406) trials evaluated third-line trifluridine/tipiracil in mCRC.^{19,20} The RECURSE trial showed superior outcomes with trifluridine/tipiracil compared with placebo, with a median OS of 7.1 vs 5.3 months (HR, 0.68; 95% CI, 0.58-0.81; $P<.001$), and a median PFS of 2.0 vs 1.7 months (HR, 0.48; 95% CI, 0.41-0.57; $P<.001$). The TERRA trial also showed superiority with trifluridine/tipiracil, demonstrating a median OS of 7.8 vs 7.1 months (HR, 0.79; 95% CI, 0.62-0.99; $P=.035$), and a median PFS of 2.0 vs 1.8 months (HR, 0.43; 95% CI, 0.34-0.54; $P<.001$). The most frequent (occurring in $\geq 5\%$ of patients) grade 3 or higher AEs in the trifluridine/tipiracil arm of the RECURSE study were neutropenia (38%), leukopenia (21%), anemia (18%), thrombocytopenia (5%); in the TERRA study these were neutropenia (33.2%), leukopenia (20.7%), anemia (17.7%), and lymphopenia (14.4%).

The efficacy and safety of the combination of trifluridine/tipiracil plus bevacizumab was established in the phase 3 SUNLIGHT trial (N=492), where it was compared with trifluridine/tipiracil alone.²¹ Median OS was significantly improved (10.8 vs 7.5 months, respectively; HR, 0.61; 95% CI, 0.49-0.77; $P<.001$), as was median PFS (5.6 vs 2.4 months, respectively; HR, 0.44; 95% CI, 0.36-0.54; $P<.001$). The most common (in $\geq 5\%$ of patients) grade 3 or higher AEs in the combination arm were neutropenia (43.1%), anemia (6.1%), and hypertension (5.7%). Neutrophil count decreased by 8.9%

The pivotal trials that evaluated fruquintinib in third-line treatment of mCRC, FRESCO and FRESCO-2, are detailed in subsequent sections.

MOA Considerations

In mCRC, the VEGF pathway has an important role in tumor angiogenesis.²⁴ The VEGF pathway is activated via signaling through 3 tyrosine kinase receptors: VEGFR-1, VEGFR-2, and VEGFR-3.²⁴ While activation of VEGFR-1 and VEGFR-2 results in signaling pathways that trigger angiogenesis, activation of VEGFR-3 pathways culminates in lymphangiogenesis.²⁴ Both have a role in mCRC progression, and inhibition of all 3 VEGFRs is an important consideration for tyrosine kinase inhibitors (TKIs).²⁴

The multi-targeted TKI regorafenib inhibits VEGFR-1, -2, and -3.¹⁴ In addition, preclinical studies have established that regorafenib also inhibits several other tyrosine kinases at clinically relevant concentrations, including RET, KIT, PDGFR- α , PDGFR- β , FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, Abl, and CSF1R.¹⁴ Attributed in part to these other target inhibitions, regorafenib has a toxicity profile that is different than that of other VEGFR-targeted TKIs.¹⁴

Fruquintinib is also a TKI that inhibits VEGFR-1, -2, and -3, resulting in a reduction of both angiogenesis and lymphangiogenesis.²⁴ However, in contrast to regorafenib (as well as other VEGFR inhibitors like sunitinib and sorafenib), fruquintinib displays limited off-target kinase activity.²⁴ For this reason, it is expected that fruquintinib can be administered at doses capable of achieving sustained VEGFR inhibition with lower toxicity compared with other multi-targeted TKIs.^{24,25}

Unlike regorafenib and fruquintinib, trifluridine/tipiracil is not a TKI but instead consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil.¹⁵ Trifluridine interferes with DNA synthesis and inhibits cell proliferation, and its available concentration is increased with the addition of tipiracil, which prevents trifluridine metabolism by thymidine phosphorylase.¹⁵

Fruquintinib in mCRC Regardless of Mutation Status

Efficacy and Safety Outcomes From FRESCO and FRESCO-2

The efficacy and safety of fruquintinib in the post-standard therapy of mCRC without targetable mutations were established in two clinical trials, FRESCO and FRESCO-2, the outcomes of which are summarized in Table 1.¹⁶

The phase 3 FRESCO study evaluated fruquintinib in 416 patients with mCRC with disease progression following 2 or more prior lines of chemotherapy.²² Patients were randomized to treatment with either fruquintinib or placebo, both administered in combination with best supportive care.²² The primary endpoint, OS, was significantly prolonged in the fruquintinib arm compared with the placebo arm (median OS 9.30 vs 6.57 months; HR, 0.65; 95% CI, 0.51-0.83; $P<.001$).²² Likewise, the secondary endpoint PFS was also significantly improved with fruquintinib versus placebo (median PFS 3.71 vs 1.84 months; HR, 0.26; 95% CI, 0.21-0.34; $P<.001$).²² Objective response rate (ORR), another secondary endpoint, was significantly higher with fruquintinib over placebo (4.7% vs 0%; $P=0.01$).²² With these efficacy results established in a Chinese population with mCRC that had progressed after 2 or more prior chemotherapy regimens, fruquintinib was approved in China.^{22,23}

Table 1. Fruquintinib: Summary of Pivotal Trials

	Trial	
	FRESCO ²²	FRESCO-2 ²³
Comparator arm	Placebo	Placebo
Patients (N)	416	691
Median OS, months, HR (95% CI)	9.3 vs 6.6 HR 0.65 (0.51-0.83) $P<.001$	7.4 vs 4.8 HR 0.66 (0.55-0.80) $P<.0001$
Median PFS, months, HR (95% CI)	3.7 vs 1.8 HR 0.26 (0.21-0.34) $P<.001$	3.7 vs 1.8 HR 0.32 (0.27-0.39) $P<.0001$
Grade ≥ 3 AEs in $\geq 5\%$ 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.

In the FRESCO study, about one-third of fruquintinib-treated patients (35.3%) experienced a dose interruption due to AEs, compared with 10.2% in the placebo arm.²² AEs resulted in dose reductions among 24.1% of fruquintinib-treated patients, compared with 4.4% of placebo-treated patients.²² A total of 15.1% of fruquintinib-treated patients discontinued fruquintinib due to an AE, compared with 5.8% of placebo-treated patients; the primary cause of discontinuation was proteinuria.²²

Importantly, over the time that the FRESCO study was conducted (between December 2014 and May 2016), neither VEGF or EGFR pathway inhibitors were part of the standard of care treatment for mCRC in China; the same was also true for regorafenib and trifluridine/tipiracil.²³ For this reason, only a small proportion of the FRESCO population had previously received a VEGF inhibitor (30%) or EGFR inhibitor (14%) prior to receiving fruquintinib; no patients were previously treated with regorafenib or trifluridine/tipiracil.²³

To evaluate fruquintinib in a Western population, a second phase 3 study (FRESCO-2) was conducted across 14 countries in North America, Europe, Asia, and Australia.²³ Patients with mCRC were eligible if they were heavily pretreated, having received all standard treatments available to them, 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.²³ A total of 691 patients were randomized 2-to-1 to receive fruquintinib or placebo, both administered with best supportive care.²³

In the FRESCO-2 population, the median age was 64

Table 2. Adverse Events Experienced by at Least 1 Patient in the Safety Population of the FRESCO-2 Study²³

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.

years (IQR, 56-70), 72% had liver metastasis, and 63% had a tumor harboring a *RAS* mutation.²³ In general, the patient population was heavily pretreated, with 73% of the population having received more than 3 prior lines of therapy and patients having a median of 4 prior lines of treatment for metastatic disease.²³ Among patients in FRESCO-2, most (96%) had received prior anti-VEGF therapy, 39% had received prior anti-EGFR therapy, and all patients had been treated with trifluridine/tipiracil (52%), regorafenib (8%), or both (39%).²³

OS, the primary endpoint of the FRESCO-2 study, was significantly prolonged in the fruquintinib arm compared with the placebo arm (median OS, 7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; $P<.0001$).²³ PFS, a key secondary endpoint, was significantly longer with fruquintinib compared with placebo (median PFS, 3.7 vs 1.8 months; HR, 0.32; 95% CI, 0.27-0.39; $P<.0001$).²³

Table 2 lists the AEs reported in the safety population of the FRESCO-2 trial. AEs resulted in dose interruption

in 47% of the fruquintinib arm compared with 27% of the placebo arm.²³ Dose reductions due to AEs occurred in 24% of fruquintinib-treated patients (vs 4% of placebo-treated patients), and were primarily a result of hand-foot syndrome (5%), hypertension (4%), and asthenia (4%).²³ The rate of discontinuation due to AEs was 20% in the fruquintinib arm and 21% in the placebo arm; the most frequent reason for fruquintinib discontinuation was asthenia (2%).²³

A meta-analysis of 12 studies evaluated the safety and efficacy of fruquintinib across single-center and multicenter studies conducted primarily in China.²⁶ Using data from 3 randomized controlled trials, both OS (HR, 0.66; 95% CI, 0.57-0.76) and PFS (HR, 0.30; 95% CI, 0.26-0.35) were found to be prolonged with fruquintinib versus placebo.²⁶ Across the 12 studies, the pooled ORR was 4.9% (95% CI, 3.2-6.6).²⁶ When limited to just the 3 randomized controlled trials, the relative risk (RR) was 7.53 (95% CI, 1.45-39.28) for fruquintinib versus placebo.²⁶

Table 3. Fruquintinib Dosing Summary per the Prescribing Information¹⁶

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

Dosing and Administration

Fruquintinib is administered at a recommended dose of 5 mg orally once daily, given on the first 21 days of each 28-day cycle.¹⁶ This starting dose can be adjusted as needed to mitigate adverse reactions, with two recommended dose reductions—first to 4 mg, then to 3 mg.¹⁶ Patients unable to tolerate the 3-mg dose should permanently discontinue fruquintinib.¹⁶ The fruquintinib capsule should be swallowed whole at about the same time each day; it can be taken with or without food.¹⁶ Treatment is continued until disease progression or unacceptable toxicity has occurred.¹⁶ Table 3 provides additional recommendations regarding dosing and administration of fruquintinib according to the prescribing information.

Managing Potential Side Effects

According to the prescribing information, grade 3 AEs are generally managed with a temporary withholding of fruquintinib and resumption at a reduced dose after resolution to grade 1 or lower.¹⁶ Typically, fruquintinib is recommended to be discontinued with grade 4 adverse reactions, although in cases of non-life-threatening toxicity, resuming fruquintinib at a lower dose is considered.¹⁶ Table 4 lists a summary of recommended dose modifications of fruquintinib according to the type of AE experienced.

The prescribing information provides additional context and recommendations for specific AEs. For example, hypertension is the most frequent AE reported with fruquintinib, occurring at a rate of 49% (19% grade 3/4) in a pooled safety population of 911 fruquintinib-treated patients.^{16,23} When beginning treatment with fruquintinib, blood pressure control at baseline is required; weekly monitoring during the first month, then monthly thereafter (and as clinically indicated) is recommended.¹⁶ Anti-hypertensive therapy is either initiated or adjusted if hypertension occurs, although dose interruption is recommended for grade 3 and

discontinuation is recommended for grade 4 events.¹⁶

Proteinuria is another frequent AE with fruquintinib, reported in 36% (2.5% grade ≥3) of the pooled safety population of 911 fruquintinib-treated patients.¹⁶ The prescribing information recommends that monitoring for proteinuria occur prior to starting fruquintinib and regularly thereafter.¹⁶ If proteinuria increases to 2 g/24 h or higher, fruquintinib is withheld until resolved (or <1 g/24 h), then resumed at the next lowest dose levels.¹⁶ If proteinuria does not recover, or if the patient develops nephrotic syndrome, fruquintinib should be permanently discontinued.¹⁶

Infections, including fatal infections, may occur with fruquintinib.¹⁶ The most frequent infections in the pooled safety population of 911 fruquintinib-treated patients 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%).¹⁶ The prescribing information recommends that fruquintinib is withheld for grade 3 or 4 infections (or worsening infection of any grade), then resumed at the same dose upon resolution of the infection.¹⁶

Hepatotoxicity may occur with fruquintinib, and grade 3 or higher increases in levels of either ALT or AST were reported in 48% of the pooled safety population of 911 fruquintinib-treated patients.¹⁶ Liver function tests (including ALT, AST, and bilirubin) should be assessed prior to starting fruquintinib, then periodically throughout treatment.¹⁶ Temporarily withholding fruquintinib is recommended in cases of hepatotoxicity, followed by dose reductions or permanent discontinuation.¹⁶

Monitoring Response to Treatment

Imaging has a critical role in assessing treatment response in patients with mCRC.²⁷ Typically, imaging involves regular

Table 4. Toxicity-Based Dose Reduction Criteria for Fruquintinib per the Prescribing Information¹⁶

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 anti-hypertensive 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 >3xULN ^a Or Bilirubin >1.5xULN ^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 >3xULN with concurrent total bilirubin >2xULN ^b	Permanently discontinue fruquintinib
	ALT/AST >20xULN ^a Or Bilirubin >10xULN ^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

^aOr baseline (instead of ULN) if baseline was abnormal. ^bIn the absence of cholestasis or hemolysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ULN, upper limit of normal.

CT scans of the chest/abdomen/pelvis with contrast; magnetic resonance imaging (MRI) may alternatively be used.²⁸ In patients with mCRC, chest/abdomen/pelvis CT is recommended by the NCCN Guidelines every 3 to 6 months over the first 2 years.¹¹ [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is not currently recommended for surveillance in mCRC.¹¹

In addition to imaging, monitoring the patient's ongoing symptoms is a clinically valuable tool that provides information both on disease progression and treatment-related toxicity.²⁹ However, symptom resolution alone, without concomitant indicators, may not be a reliable assessment of treatment response, particularly in the third-line when disease stabilization is often a primary goal.^{29,30}

Tumor biomarkers can also provide important information regarding treatment response. Serial carcinoembryonic antigen (CEA) monitoring is recommended in the NCCN Guidelines every 3 to 6 months for the first 2 years.¹¹ While circulating tumor DNA (ctDNA), evaluated via liquid biopsy, is not currently recommended as a surveillance or monitoring tool, emerging evidence suggests that ctDNA may be useful for assessing responses to systemic therapy, with evidence that rising ctDNA levels may precede radiological recurrence.^{31,32}

Bringing It All Together

For patients with mCRC who have undergone prolonged

exposure to combination chemotherapy, nonchemotherapy options such as TKIs represent an important therapeutic alternative. After multiple lines of cytotoxic therapy, cumulative toxicities can negatively affect patient QOL and functional status.^{33,34} AEs remain a key consideration when selecting among available therapies, as toxicity burden can significantly influence a patient's daily functioning and overall treatment experience.^{35,36}

In the third-line setting and beyond, treatment decisions should be guided by shared decision-making that incorporates the patient's goals, preferences, tolerance for potential toxicities, likely impact on QOL, alongside efficacy and safety data from clinical trials. In the absence of validated predictive biomarkers to guide selection among approved later-line agents, clinicians must individualize therapy based on clinical characteristics, comorbidities, prior treatment exposures, and patient-centered priorities.

In the case of SB, a 72-year-old man with *KRAS*-mutated mCRC who experienced long-lasting benefit from CAPEOX plus bevacizumab followed by FOLFIRI, the transition to a non-chemotherapy option was driven by the need to reduce cumulative toxicity while helping to maintain disease control. Available post-standard therapies, including fruquintinib, regorafenib, and trifluridine/tipiracil with or without bevacizumab, offer differing toxicity profiles, mechanisms of action, and dosing considerations.

Fruquintinib is a selective oral inhibitor of VEGFR-1, -2, and -3 with limited off-target kinase activity.²⁴ This selectivity distinguishes it from earlier generation TKIs.¹⁴

The phase 3 FRESKO and FRESKO-2 studies demonstrated that fruquintinib improves OS and PFS in heavily pre-treated mCRC across diverse patient subgroups, including those defined by age, performance status, *RAS* mutation status, primary tumor site, and presence of liver metastases.^{22,23} Although AEs were more common with fruquintinib than with placebo, they were generally manageable with dose withholding or reduction.²³

Based on these data and SB's clinical history, fruquintinib was selected due to its tolerability profile, demonstrated activity in refractory *KRAS*-mutant disease, and compatibility with bevacizumab, to which he had previously responded. SB has achieved a rapid hepatic response with only mild and manageable hypertension, and remains on treatment, underscoring the value of individualized, evidence-informed therapy selection in later-line mCRC.

Disclosures

Dr Hussein has performed consulting or advisory role for AbbVie, AstraZeneca, AVEO, BeiGene, Bristol Myers Squibb/Celgene, E.R. Squibb & Sons, LLC, Incyte, Janssen Biotech, Janssen Scientific Affairs, Johnson & Johnson/Janssen, MorphoSys, PharmaEssentia, Pfizer, and Stemline Therapeutics.

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Important Safety Information and Indication – Professional

INDICATION

FRUZAQLA 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Hypertension** occurred in 49% of 911 patients with mCRC treated with FRUZAQLA, including Grade 3-4 events in 19%, and hypertensive crisis in three patients (0.3%). Do not initiate FRUZAQLA unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first month and at least monthly thereafter as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue FRUZAQLA based on severity of hypertension.
- **Hemorrhagic Events** including serious, fatal events can occur with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 6% of patients experienced gastrointestinal hemorrhage, including 1% with a Grade ≥3 event and 2 patients with fatal hemorrhages. Permanently discontinue FRUZAQLA in patients with severe or life-threatening hemorrhage. Monitor the International Normalized Ratio (INR) levels in patients receiving anticoagulants.
- **Infections.** FRUZAQLA can increase the risk of infections, including fatal infections. In 911 patients with mCRC treated with FRUZAQLA, the most common infections 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%). Withhold FRUZAQLA for Grade 3 or 4 infections, or worsening infection of any grade. Resume FRUZAQLA at the same dose when the infection has resolved.
- **Gastrointestinal Perforation** occurred in patients treated with FRUZAQLA. In 911 patients with mCRC treated with FRUZAQLA, 1.3% experienced a Grade ≥3 gastrointestinal perforation, including one fatal event. Permanently discontinue FRUZAQLA in patients who develop gastrointestinal perforation or fistula.
- **Hepatotoxicity.** FRUZAQLA can cause liver injury. In 911 patients with mCRC treated with FRUZAQLA, 48% experienced increased ALT or AST, including Grade ≥3 events in 5%, and fatal events in 0.2% of patients. Monitor liver function tests (ALT, AST, and bilirubin) before initiation and periodically throughout treatment with FRUZAQLA. Temporarily hold and then reduce or permanently discontinue FRUZAQLA depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests.
- **Proteinuria.** FRUZAQLA can cause proteinuria. In 911 patients with mCRC treated with FRUZAQLA, 36% experienced proteinuria and 2.5% of patients experienced Grade ≥3 events. Monitor for proteinuria before initiation and periodically throughout treatment with FRUZAQLA. For proteinuria ≥2g/24 hours, withhold FRUZAQLA until improvement to ≤Grade 1 proteinuria and resume FRUZAQLA at a reduced dose. Discontinue FRUZAQLA in patients who develop nephrotic syndrome.
- **Palmar-Plantar Erythrodysesthesia (PPE)** occurred in 35% of 911 patients treated with FRUZAQLA, including 8% with Grade 3 events. Based on severity of PPE, withhold FRUZAQLA and then resume at the same or reduced dose.
- **Posterior Reversible Encephalopathy Syndrome (PRES),** a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 911 patients treated with FRUZAQLA. Perform an evaluation for PRES in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FRUZAQLA in patients who develop PRES.

- **Impaired Wound Healing.** In 911 patients with mCRC treated with FRUZAQLA, 1 patient experienced a Grade 2 event of wound dehiscence. Do not administer FRUZAQLA for at least 2 weeks prior to major surgery. Do not administer FRUZAQLA for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of FRUZAQLA after resolution of wound healing complications has not been established.
- **Arterial Thromboembolic Events.** In 911 patients with mCRC treated with FRUZAQLA, 0.8% of patients experienced an arterial thromboembolic event. Initiation of FRUZAQLA in patients with a recent history of thromboembolic events should be carefully considered. In patients who develop arterial thromboembolism, discontinue FRUZAQLA.
- **Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF).** FRUZAQLA 1 mg capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. FRUZAQLA 1 mg contains FD&C Yellow No. 6 (sunset yellow FCF), which may cause allergic reactions.
- **Embryo-Fetal Toxicity.** Based on findings in animal studies and its mechanism of action, FRUZAQLA can cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to a fetus.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) following treatment with FRUZAQLA included hypertension, palmar-plantar erythrodysesthesia (hand-foot skin reactions), proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.

DRUG INTERACTIONS: Avoid concomitant administration of FRUZAQLA with strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with FRUZAQLA and for 2 weeks after the last dose.
- **Females and Males of Reproductive Potential**
 - **Pregnancy Testing:** Verify pregnancy status of females of reproductive potential prior to initiating FRUZAQLA.
 - **Contraception:** Females of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment and for 2 weeks after the last dose of FRUZAQLA.
 - **Infertility:** Advise females of reproductive potential that FRUZAQLA may cause post-implantation loss.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-844-662-8532 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see FRUZAQLA (fruquintinib) full Prescribing Information <https://www.fruzaqla.com/sites/default/files/resources/fruzaqla-prescribing-information.pdf>



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