Multikinase Inhibitors in Refractory Metastatic Colorectal Cancer: An Optimal Sequence?

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Abstract: Despite major advances in management strategies, metastatic colorectal cancer remains an important clinical challenge because most patients experience progression after standard first- and second-line treatments. In the setting of refractory disease, defined as disease that progresses after 2 or more lines of treatment, the therapeutic landscape is growing. Options include regorafenib, trifluridine plus tipiracil (FTD/TPI) with or without bevacizumab, and fruquintinib, all of which received approval from the US Food and Drug Administration after showing modest survival benefits in phase 3 trials. However, optimal sequencing remains undefined owing to the absence of direct comparative studies. Real-world data suggest that sequencing regorafenib before FTD/TPI may improve outcomes, with the addition of bevacizumab to FTD/TPI offering further survival benefit. Fruquintinib has also shown efficacy after the use of regorafenib and/or FTD/TPI. Therefore, treatment decisions are based on a case-by-case scenario, with factors such as comorbidities, preferred route of administration, and tolerability taken into consideration. Additionally, improved patient stratification with biomarker testing has become essential for guiding personalized treatment selection. This review highlights the current evidence and gaps in sequencing strategies for the treatment of refractory metastatic colorectal cancer, highlighting the need for future research to inform personalized, effective, and sustainable treatment pathways.

Keywords
Bevacizumab, fruquintinib, metastatic colorectal cancer, regorafenib, tipiracil, trifluridine

Introduction

Colorectal cancer (CRC) is the third most common type of cancer in

Table 1. General Overview of Key Clinical Trials, Efficacy Outcomes, and Frequent Toxicities of Trifluridine/Tipiracil With and Without Bevacizumab, Regorafenib, and Fruquintinib

Third-line agent	Comparator	Study ID	Phase	Median OS, mo	Grade 3-4 toxicity, %	Discontinuation rate, %	Most common treatment-related toxicities, %
FTD/TPI	Placebo	TERRA	3	7.8 vs 7.1	45.8 vs 10.4	10 vs 9.6	Neutropenia: 67.2 vs 0.7 Anemia: 77.1 vs 38.5 Thrombocytopenia: 35.4 vs 7.4
		RECOURSE	3	7.1 vs 5.3	69 vs 52	3.9 vs 1.9	Anemia: 77 vs 33 Neutropenia: 67 vs <1 Thrombocytopenia: 42 vs 8 Fatigue: 35 vs 23
		Yoshino et al	2	9 vs 6.6	NR	NR	Anemia: 73 vs 16 Neutropenia: 72 vs 2 Fatigue: 58 vs 42
FTD/TPI + bevacizumab	FTD/TPI	SUNLIGHT	3	10.8 vs 7.5	72.4 vs 69.5	12.6 vs 12.6	Neutropenia: 62.2 vs 51.2 Anemia: 28.9 vs 31.7 Fatigue: 21.5 vs 16.3
		Pfeiffer et al	2	9.4 vs 6.7	NR	2 vs 4	Fatigue: 85 vs 85 Neutropenia: 84.2 vs 66 Anemia: 72 vs 67
Regorafenib + BSC	Placebo	CORRECT	3	6.4 vs 5	54 vs 14	NR	HSFR: 47 vs 8 Fatigue: 47 vs 28 Diarrhea: 34 vs 8
		CONCUR	3	8.8 vs 6.3	54 vs 14	14 vs 6	HSFR: 73 vs 4 HTN: 23 vs 4 Diarrhea: 18 vs 2
Fruquintinib	Placebo	FRESCO	3	9.3 vs 6.6	46 vs 7.3	15.1 vs 5.8	HTN: 55.4 vs 15.3 HSFR: 49.3 vs 2.9 Diarrhea: 20.1 vs 2.2
		FRESCO-2	3	7.4 vs 4.8	63 vs 50	20 vs 20.1	HTN: 37 vs 9 Diarrhea: 24 vs 10 Fatigue: 20 vs 16

BSC, best supportive care; FTD/TPI, trifluridine/tipiracil; HSFR, hand-foot skin reaction; HTN, hypertension; mo, months; NR, not reported; OS, overall survival.

the United States, with an estimated 153,000 new cases in 2023, accounting for 8% of all new cancer diagnoses.[1] At the time of diagnosis, approximately 23% of patients with CRC have metastatic disease, which carries a poor prognosis; metastatic CRC (mCRC) is associated with a 5-year survival rate of 15%.[2] Nevertheless, substantial progress has been made with the identification of actionable biomarkers, the introduction of targeted therapies, and advances in the surgical resection of metastases, all of which have contributed to the adoption of a multimodal and personalized treatment strategy that has extended median overall survival (mOS) to approximately 30 months.[3-7] Despite these advancements, the management of mCRC continues to present clinical challenges to providers and health systems. Patients experience disease progression after first- and second-line treatments with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy with or without targeted therapy, and they may require additional lines of treatment. After progressing on 2 lines of therapy, mCRC is considered refractory to standard therapies. Currently approved agents for refractory mCRC include regorafenib (Stivarga, Bayer HealthCare), trifluridine/tipiracil (FTD/TPI; Lonsurf, Taiho Oncology) with or without bevacizumab,

and fruquintinib (Fruzaqla, Takeda). Despite a growing number of treatment options available in the refractory setting, evidence to determine the appropriate treatment sequence, one that can provide the most meaningful clinical benefit for patients with refractory mCRC, is lacking. Because real-world data have shown that drug sequencing may affect the overall outcomes of patients with mCRC in first- and second-line treatment, we aim to explore sequencing strategies in the setting of refractory mCRC.[8]

Mechanisms of Action

Angiogenesis, the process in which new blood vessels form from existing vasculature, is a complex mechanism that plays a crucial role in tumor cell growth and metastasis. The vascular endothelial growth factor (VEGF) pathway consists of 6 ligands and 3 VEGF receptors (VEGFRs), with VEGF-A the ligand of interest in this context. VEGF-A binds to VEGFR 1 and VEGFR 2, stimulating endothelial cell differentiation, migration, growth, and survival.[9] Drugs targeting VEGF or VEGFR can be divided into 2 main groups: monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). mAbs include bevacizumab, a humanized antibody against all isoforms of VEGF-A; ramucirumab (Cyramza, Lilly), a humanized antibody against VEGFR 2; and aflibercept, a decoy receptor binding VEGF-A. Among these, bevacizumab has shown the greatest efficacy in refractory mCRC when combined with FTD/TPI.[10] TKIs such as regorafenib and fruquintinib inhibit angiogenesis by binding to the intracellular kinase domain of various receptors involved in the angiogenic process. Regorafenib is an oral TKI that targets angiogenesis (VEGFRs 1-3, TIE2), oncogenesis (KIT, RET, BRAF), and the tumor microenvironment (platelet-derived growth factor receptors and fibroblast growth factor receptor). Fruquintinib is a selective VEGFR inhibitor that specifically targets VEGFR 1, VEGFR 2, and VEGFR 3 to inhibit tumor angiogenesis. These drugs have such a diverse array of targets that they have been shown to be difficult to tolerate even as monotherapy, and patients often require dose modifications.[11,12] As outcomes have improved over the past decade, more patients are eligible to receive treatments in the third-line setting and beyond. As such, future treatments must prioritize tolerability and quality of life.

Regorafenib

Regorafenib was approved by the US Food and Drug Administration (FDA) in 2012 as a treatment option following progression after 2 or more lines of therapy including a fluoropyrimidine, oxaliplatin, irinotecan, and biologic therapies (anti-VEGF or anti-EGFR therapy). Approval was based on the CORRECT trial,[13,14] a randomized, double-blinded phase 3 study comparing the efficacy of regorafenib with that of placebo in patients with mCRC previously treated with standard therapies. In this trial, regorafenib led to a significant increase in mOS, at 6.4 vs 5.0 months (hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; P=.0052; Table 1) and a modest improvement in median progression-free survival (mPFS), at 1.9 vs 1.7 months (HR, 0.49; 95% CI, 0.42-0.58; P<.0001). In the subsequent CONCUR study, which unlike the CORRECT study enrolled Asian patients with refractory mCRC who had not received prior treatment with anti-EGFR or anti-VEGF agents, regorafenib was still superior to placebo.[15] However, both trials reported that regorafenib was associated with treatment-related adverse events (TRAEs) in more than 90% of patients. Roughly 50% of the patients receiving regorafenib experienced grade 3 or higher TRAEs, and dose reductions were required in more than 60% of cases, especially within the first 2 cycles. Side effects of regorafenib most commonly included hand-foot skin reaction, hypertension, fatigue, diarrhea, and laboratory abnormalities. Accordingly, the dosing schedule used in the Regorafenib Dose Optimization Study (ReDOS)—which consisted of 80 mg/d orally with weekly escalation in 40-mg increments to 160 mg/d—was associated with a more tolerable side effect profile.[16] In a systematic review and meta-analysis that included ReDOS, RECOURSE, CONCUR, CORRECT, TERRA, and a phase 2 study from Yoshino and colleagues, a trend toward improved mOS was observed when the regorafenib dose escalation strategy was compared with regorafenib at 160 mg/d or FTD/TPI, suggesting that the dose escalation strategy might be a better option than FTD/TPI and regorafenib at 160 mg/d.[17]

Trifluridine/Tipiracil

FTD/TPI is an oral fluoropyrimidine, similar to 5-fluorouracil, that consists of the thymidine-based cytotoxic nucleoside analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil hydrochloride, which improves the bioavailability of trifluridine to counteract secondary resistance.[18] FTD/TPI was approved by the FDA in 2015 on the basis of the RECOURSE trial, which compared FTD/TPI with placebo in patients who had refractory mCRC.[19] In this trial, FTD/TPI was associated with a longer mOS (7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58-0.81; P<.0001) and a modest improvement in mPFS (2.0 vs 1.7 months; HR, 0.48; 95% CI, 0.41-0.57; P<.0001) in comparison with placebo. Grade 3 or higher TRAEs occurred in 69% of patients receiving FTD/TPI and in 52% of the placebo group. Neutropenia was the most common TRAE (grade ≥3 in 38% of patients), and

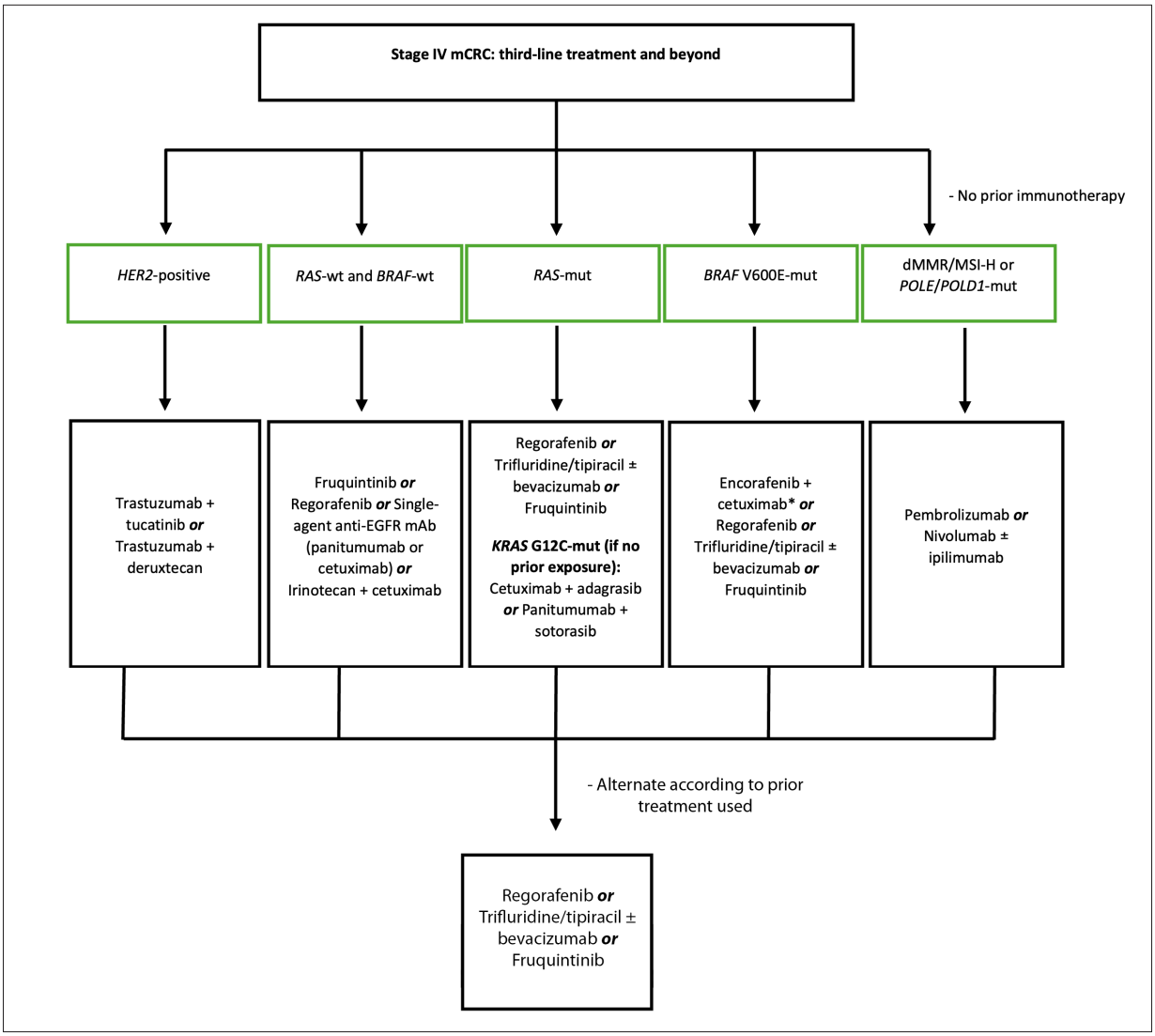

Figure. Options for third-line treatment and beyond in metastatic colorectal cancer, according to molecular profile.

*Not an option in patients who received modified leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX6) plus encorafenib and cetuximab as a first-line treatment, according to the BREAKWATER trial.

dMMR, mismatch repair–deficient; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; mut, mutated; RAS, rat sarcoma; wt, wild-type.

hematologic side effects (neutropenia, anemia, febrile neutropenia) led to dose reductions in 14% of cases. The TERRA trial, a similar study conducted in Asia, had efficacy and safety results comparable with those of RECOURSE; however, key differences should be noted; in RECOURSE, 17% of patients had prior regorafenib exposure, whereas in TERRA, patients had no prior exposure to anti-VEGF or anti-EGFR therapy.[20] In a subgroup analysis of the patients in RECOURSE who had prior exposure to regorafenib, their OS benefit from FTD/TPI (HR, 0.69; 95% CI, 0.45-1.05) was similar to the OS benefit in the patients who did not receive prior regorafenib (HR, 0.69; 95% CI, 0.57-0.83). The addition of bevacizumab to FTD/TPI significantly improved mOS (10.8 vs 7.5 months; HR, 0.61; 95% CI, 0.49-0.77; *P*<.001) and mPFS (5.6 vs 2.4 months; HR, 0.44; 95% CI, 0.36-0.54; *P*<.001) in comparison with FTD/TPI alone, as reported in the phase 3 SUNLIGHT trial.[10] Notably, this significant improvement was seen regardless of prior bevacizumab use, although mPFS and mOS were numerically longer in the patients who did not receive bevacizumab in prior lines of therapy than in

those who did (mPFS: HR, 0.29; 95% CI, 0.19-0.43 vs HR, 0.51; 95% CI, 0.41-0.63; mOS: HR, 0.72; 95% CI, 0.56-0.92 vs HR, 0.40; 95% CI, 0.25-0.63). Regardless, the National Comprehensive Cancer Network (NCCN) added FTD/TPI with or without bevacizumab as a treatment option for patients with refractory mCRC, favoring the combination with bevacizumab.[21,22]

Fruquintinib

Fruquintinib is a selective VEGFR inhibitor that specifically targets VEGFR 1, VEGFR 2, and VEGFR 3 to inhibit tumor angiogenesis. Safety and efficacy were evaluated in 2 phase 3 trials: FRESCO and FRESCO-2.[23,24] In the FRESCO trial, conducted in China, patients with refractory mCRC who had not received prior VEGFR inhibitor therapy were randomized to receive either fruquintinib or placebo. Patients in the fruquintinib arm had significantly longer mOS (9.3 vs 6.6 months; HR, 0.65; 95% CI, 0.51-0.83; P<0.001) and PFS (3.7 vs 1.8 months; HR, 0.26; 95% CI, 0.21-0.34; P<.001) than did those who received placebo.[23] FRESCO-2, an international multicenter study comparing fruquintinib with placebo, enrolled patients who had received a median of at least 4 previous lines of systemic therapy consisting of chemotherapy, targeted therapies, FTD/TPI, and/or regorafenib.[24] In comparison with the patients in FRESCO, 97% of the patients in FRESCO-2 received prior VEGF inhibitor therapy, and nearly half had disease progression on both FTD/TPI and regorafenib. The mOS was 7.4 months with fruquintinib vs 4.8 months with placebo (HR, 0.66; 95% CI, 0.55-0.80; P<.0001). Grade 3 or higher AEs occurred in 63% of the patients who received fruquintinib and in 50% of those who received placebo. The most common grade 3 or higher AEs were hypertension (14%), asthenia (8%), and hand-foot syndrome (6%). On the basis of these results, the NCCN panel recommends fruquintinib as a treatment option for patients with mCRC that has progressed after treatment with all other available regimens. Fruquintinib can be given before or after either regorafenib or FTD/TPI with or without bevacizumab.[22]

Sequencing Considerations in the Third-Line Setting

With more targeted therapies becoming available in clinical practice in mCRC, molecular testing for key biomarkers such as *KRAS* G12 mutations, human epidermal growth factor receptor 2 amplification, *BRAF* V600E mutations, mismatch repair protein deficiency, and high microsatellite instability is recommended for the management of mCRC (Figure). Collectively, these biomarkers account for only 15% to 20% of all patients with mCRC, and as such, most patients will require regorafenib, fruquintinib, and/or trifluridine/tipiracil with or without bevacizumab. Table 1 summarizes the key clinical trials addressing the safety and efficacy of these 3 agents.

Despite the expansion of available treatments in this setting, no formal head-to-head comparisons of regorafenib, FTD/TPI with or without bevacizumab, and/or fruquintinib have been conducted. Because most patients qualify for additional lines of therapy with the observed improved outcomes in the first and second lines,[25] managing optimal sequencing has become increasingly complex. Appropriate treatment sequencing allows patients to receive all available agents, which may improve outcomes.[26] Consequently, the need for data that address the most effective sequencing strategies for mCRC is growing.

In the RECOURSE trial, the HRs for OS were similar in the subgroup of patients who received regorafenib before FTD/TPI and those who received FTD/TPI only (HR, 0.69; 95% CI, 0.45-1.05), suggesting that mOS benefit may be similar regardless of the sequence of administration.[19] Additionally, a systematic review and network meta-analysis conducted before the approval of fruquintinib, which compared survival outcomes with regorafenib vs those with FTD/TPI, showed no statistically significant differences in mOS and mPFS, with different safety profiles.[17] In the absence of formal sequencing guidelines, informed decisions can be supported by comparative evaluations of real-world effectiveness.[22] For instance, treatment adherence and persistence were significantly higher in patients receiving FTD/TPI than in patients on regorafenib, and treatment adherence was likely to be improved in patients who switched from FTD/TPI to regorafenib (odds ratio, 2.91 for medication possession ratio ≥80% and 4.60 for proportion of days covered ≥80%; P<.001) than in those who switched from regorafenib to FTD/TPI.[27] Additionally, another real-world study conducted in Japan observed longer mPFS in patients exposed to regorafenib before FTD/TPI compared with those who received FTD/TPI without prior regorafenib.[28] Similar findings were reported in a multicenter study from Italy, in which mPFS and mOS were significantly longer in patients receiving regorafenib followed by FTD/TPI than in those receiving the reverse sequence (mPFS: 11 vs. 8.5 months; HR, 0.62; 95% CI, 0.46-0.83; P=.0014; mOS: 14.9 vs 13 months; HR, 0.70; 95% CI, 0.51-0.96; P=.0296).[29] Therefore, regorafenib appears to provide greater benefit when it is used earlier in the treatment sequence and is followed by FTD/TPI, although this finding needs to be confirmed in prospective randomized trials.

The sequence of regorafenib followed by FTD/TPI

Table 2. Cost of a 28-Day Cycle of Regorafenib, Fruquintinib, Trifluridine/Tipiracil, and Bevacizumab

Medication	Cost, 28-day cycle
Regorafenib[34]	$28,612.08*
Fruquintinib[34]	$31,616.34**
Trifluridine/tipiracil3[4]	$24,420.40***
Bevacizumab3[5]	$6209.17****

*Based on FDA-labeled dose of 160 mg PO daily days 1-21 of each 28-day cycle.

**Based on FDA-labeled dose of 5 mg PO daily days 1-21 of each 28-day cycle.

***Assuming average body surface area[36] of 2 m^2, 35 mg/m^2 PO twice daily days 1-5 and days 8-12 of each 28-day cycle.

****Assuming average 85-kg patient, 5 mg/kg IV once every 14 days.[36]

FDA, US Food and Drug Administration; IV, intravenously; PO, orally.

was not significantly affected by the addition of bevacizumab to FTD/TPI, as seen in a retrospective cohort study comparing sequential treatment with regorafenib followed by FTD/TPI with or without bevacizumab (R-T) vs the reverse sequence (T-R).[30] The mOS was numerically longer for R-T than for T-R, although the difference was not statistically significant (OS, 13.1 vs 11.5 months; HR, 0.94; 95% CI, 0.74-1.19).[30] Benefit from regorafenib appears to be greater in patients who have not previously received bevacizumab than in those who have previously received bevacizumab therapy. In CONCUR, for example, the HR for OS was 0.99 (95% CI, 0.48-2.03) in patients with previous anti-VEGF use and was 0.31 (95% CI, 0.19-0.53) in patients with no previous targeted therapy.[15]

A main limitation of the recently published FRESCO-2 study is that fruquintinib was compared with placebo rather than with standard-of-care FTD/TPI or regorafenib, leaving the question of which agent is superior in the refractory setting unanswered.[24] Despite this limitation, the study allowed prior regorafenib and/or FTD/TPI, and fruquintinib was still superior to placebo (HR for prior FTD/TPI: 0.367; 95% CI, 0.287-0.470; HR for prior regorafenib: 0.292; 95% CI, 0.139-0.611; and HR for both: 0.285; 95% CI, 0.212-0.382). As such, the administration of regorafenib, FTD/TPI, or both before fruquintinib seems to result in comparable outcomes. Additionally, data on treatment sequencing including fruquintinib are limited to 2 real-world observational studies based in China. Both studies show that mOS may be longer with regorafenib followed by fruquintinib than with the reverse (28.1 vs 18.4 months; *P*=.024; and 15.0 vs 8.3 months; *P*=.019).[31,32] A post hoc analysis from FRESCO and FRESCO-2 found similar improvements in mOS and mPFS with fruquintinib regardless of the sequence of prior FTD/TPI or regorafenib and the number of prior therapies.[33] Overall, this evidence remains limited, and prospective data are required to determine the optimal sequencing in third- or later-line therapy for mCRC to maximize benefit for patients. As such, treatment decisions are based on a case-by-case scenario, with comorbidities, prior treatment toxicities, performance status, age, patient preferences, and cost taken into account (Table 2). For example, for a patient with a preference for an oral-only therapy or with significant myelotoxicity due to prior cytotoxic therapy, one may favor regorafenib or fruquintinib over FTD/TPI. On the other hand, one may favor FTD/TPI with or without bevacizumab for a patient with prior significant skin toxicity.

Conclusion

As the landscape of treatment options for refractory mCRC expands, the need to develop informed strategies for optimal therapy sequencing is pressing. With the FDA approval of fruquintinib, FTD/TPI with or without bevacizumab, and regorafenib, comparative trials are necessary to guide decisions regarding treatment sequencing. Ongoing trials will identify new agents and combinations, and as such, best practices for the treatment of mCRC will continue to evolve. Ultimately, emphasis must be placed on integrating emerging data to tailor treatment strategies according to each patient's clinical status and treatment history, while cost-effectiveness is also considered. Moving forward, it will be crucial to identify predictive biomarkers and develop new therapeutic combinations with more favorable risk-benefit profiles.

Disclosures

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data and safety monitoring boards for The Valley Hospital, FibroGen, Kintor Pharma, AstraZeneca, Exelixis, Merck/Eisai, Pancreatic Cancer Action Network (PanCAN), and 1Globe Health Institute. He is a member of the Scientific Advisory Boards of Imugene, Immuneering, Xilis, Replimune, Artiva Biotherapeutics, and Sun Pharma. He reports the following inventions/patents: WO/2018/183488 and WO/2019/055687. Drs Hoyek, Pirozzi, Bauernfeind, and Jones have no financial relationships to disclose.

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