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Improving Survival in Metastatic Colorectal Cancer Through Optimized Patient Selection

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Abstract: The systemic treatment options for patients with metastatic colorectal cancer have recently expanded with the US Food and Drug Administration approval of fruquintinib being added to previously approved trifluridine/tipiracil with or without bevacizumab and regorafenib. These therapies are recommended for use based on the initial clinical trials that focused on their safety and efficacy in extending overall survival of patients with refractory metastatic disease, as well as later studies, including the ReDOS study that confirmed the dose-escalation strategy of regorafenib to be key in optimizing duration of therapy and preventing side effects. Although more research is needed on how to sequence third-line therapies, data from real-world studies showed that switching from regorafenib to trifluridine/tipiracil with or without bevacizumab allowed patients to have a chemotherapy-free break and led to improved survival, suggesting that there may be a benefit for using regorafenib first. Current treatment guidelines state that each therapy can be given before or after the others. Generally, sequencing considerations in the refractory setting include multiple variables such as tumor characteristics, toxicities, factors that are important to the patient, response to prior lines of therapy, and extent of disease.



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Review of Third-Line Treatment Strategies in Refractory Metastatic Colorectal Cancer

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The treatment of refractory metastatic colorectal cancer (mCRC) has seen significant growth over the past decade. The landscape of refractory mCRC care changed with the US Food and Drug Administration (FDA) approval of regorafenib, trifluridine/tipiracil with or without bevacizumab, and fruquintinib for use in the third-line setting. Common among these 3 therapies is the targeting of the vascular endothelial growth factor (VEGF) pathway, highlighting the importance of this pathway in the pathology of mCRC.

Regorafenib

Regorafenib is FDA-approved for the treatment of mCRC; it is indicated for patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if the disease is RAS wild-type, an anti-epidermal growth factor receptor (anti-EGFR) therapy.1 Considered a chemotherapy-free approach to treat mCRC, regorafenib is a small-molecule inhibitor of multiple kinases. Regorafenib, or its major active metabolites, inhibits the following kinases at physiologic concentrations: RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, SAPK2, PTK5, Abl, and CSF1R. In vivo animal model testing has confirmed the antiangiogenic, antimetastatic, and anti–tumor growth activities of regorafenib. The efficacy and safety of regorafenib in the third-line setting were established in 2 clinical trials: CORRECT and CONCUR.

CORRECT was a randomized, double-blind, placebo-controlled, phase 3 clinical trial investigating regorafenib as a treatment for mCRC that had progressed following treatment with all standard therapies approved at the time.² CORRECT was an international trial that recruited patients from North America, Europe, Asia, and Australia; therefore, the approved standard therapies varied but had to include as many of the following as were licensed locally: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, plus either cetuximab or panitumumab (in patients with *KRAS* wild-type mCRC).

In CORRECT, patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were randomized to treatment with either 160 mg of regorafenib (n=505) or matching placebo (n=255) administered once daily for the first 3 weeks of a 4-week cycle. Randomized patients were stratified by prior treatment with VEGF-targeting drugs (yes or no), time from diagnosis of metastatic disease (\geq 18 or <18 months), and geographic region. Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or physician decision. Patients in both arms were allowed to receive best supportive care.

Baseline characteristics were generally similar across the regorafenib and placebo arms. One exception was the proportion of patients with a KRAS mutation (54% vs 62% in the regorafenib and placebo arms, respectively). The median age in both arms was 61 years. Most patients (83% in each arm) were from North America, western Europe, Israel, or Australia; 14% were from Asia and 3% from eastern Europe. The primary disease site was the colon in 64% (regorafenib) and 68% (placebo) of cases, and the histology was adenocarcinoma in the vast majority of cases (98% and 96%, respectively). At baseline, 49% of patients in the regorafenib arm and 47% in the placebo arm had received 4 or more prior systemic therapies, 25% and 28% had received 3 prior systemic therapies, and 27% and 25% had received 1 or 2 prior systemic therapies.

Overall survival (OS), the primary endpoint of the CORRECT study, was met at the second planned interim analysis, with a significantly prolonged median OS in a comparison of the regorafenib arm with the placebo arm (6.4 vs 5.0 months; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; P=.0052). The OS benefit with regorafenib was observed across nearly all patient subgroups, including age group (<65 vs ≥65 years), sex (male vs female), region (North America, western Europe, Israel, and Australia, vs Asia, vs eastern Europe), and number of prior lines of therapy (≤3 vs >3). One exception was the effect in patients whose primary disease site was the colon (HR, 0.70; 95% CI, 0.56-0.89) vs the rectum (HR, 0.95; 95% CI, 0.63-1.44); however, this subgroup analysis was limited by the small number of patients.

Progression-free survival (PFS), the secondary endpoint, showed a clear separation in the Kaplan-Meier curves that occurred after the median PFS had been reached. Median PFS was significantly longer with regorafenib than with placebo (1.9 vs 1.7 months; HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001). The overall response rate, another secondary endpoint, was low in both arms (1.0% with regorafenib and 0.4% with placebo), and no complete responses occurred. However, the disease control rate (DCR), which included those patients who achieved stable disease in addition to patients achieving a response, was significantly higher in the regorafenib arm than in the placebo arm (41% vs 15%; *P*<.0001).

A large proportion of patients in the regorafenib arm (67%) required a dose modification because of an adverse event (AE), vs 23% in the placebo arm. Dose modifications in the regorafenib arm included both dose reductions (38%) and dose interruptions (61%). Most AEs were reported during the first or second treatment cycle. The most frequently reported AEs of any grade in the regorafenib arm were fatigue and hand-foot skin reaction, each occurring in 47% of the regorafenib-treated patients. Grade 3 or 4 treatment-related AEs were more common in the regorafenib arm than in the placebo arm (54%) vs 14%, respectively). The most common regorafenib-related grade 3 or higher AEs were hand-foot skin reaction (17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash or desquamation (6%).

The similarly designed CONCUR study was a randomized, double-blind, placebo-controlled, parallel group, phase 3 trial 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.³ However, unlike the CORRECT study, the CONCUR study permitted the inclusion of patients who had not been treated with a biologic agent because these agents were not widely available in some Asian countries at the time of the trial.

Overall, 40% of the CONCUR study population had not previously received any targeted biologic agent.

At randomization, patients were stratified by the number of metastatic sites (single vs multiple organs) and time from diagnosis of metastatic disease (<18 vs \geq 18 months). Patients were treated with either 160 mg of regorafenib (n=136) or matching placebo (n=68); both treatments were administered daily for the first 3 weeks of a 4-week cycle. Patients in both treatment arms were also allowed best supportive care. Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the treating physician.

Compared with the population of the CORRECT trial, the CONCUR study population was slightly younger (median age, 56.5 years). At baseline, 63% of the study population had received 3 or more lines of treatment for mCRC, and just over half of the patients had received 4 or more prior systemic therapies (54% in the regorafenib arm and 51% in the placebo arm).

OS, the primary endpoint of the CONCUR trial, was met. Median OS was significantly longer in the regorafenib arm than in the placebo arm (8.8 vs 6.3 months; HR, 0.55; 95% CI, 0.40-0.77; 1-sided P=.00016). In an exploratory analysis of the effect of prior treatment with a biologic therapy, it was apparent that the OS benefit with regorafenib was larger in the patients who were less heavily pretreated, particularly with biologic agents.

The secondary endpoint of median PFS was also longer in the regorafenib arm than in the placebo arm (3.2 vs 1.7 months; HR, 0.31; 95% CI, 0.22-0.44; 1-sided P<.0001). As in the CORRECT trial, the overall response rate was low (4% with regorafenib and 0% with placebo; 1-sided P=.045), and no complete responses were observed. The DCR including patients with stable disease was significantly higher with regorafenib than with placebo (51% vs 7%, respectively; 1-sided P<.0001).

AEs led to treatment discontinuation in 14% of patients in the regorafenib arm and 6% of patients in the placebo group; most discontinuations were owing to laboratory events. Treatment modifications (including treatment interruption, dose reduction, or both) were required in 71% of patients in the regorafenib arm because of an AE but in just 16% of placebo-treated patients. The rate of treatment-related grade 3 or higher AEs was higher with regorafenib than with placebo (54% vs 15%). Of these, the most frequently reported were hand-foot skin reaction, hypertension, hyperbilirubinemia, hypophosphatemia, alanine aminotransferase concentration increase, aspartate aminotransferase concentration increase, lipase concentration increase, and maculopapular rash.

Since the publication of these 2 major trials, other, smaller studies have been published that support the use



Figure 1. ReDOS: Overall survival (top) and progression-free survival (bottom) in the dose-escalation and standard dosing regorafenib treatment arms. Adapted from Bekaii-Saab TS et al. *Lancet Oncol.* 2019;20(8):1070-1082.⁷

of regorafenib in patients with refractory mCRC. For example, CONSIGN was a large, single-arm, open-label phase 3b trial designed to further evaluate the safety of regorafenib in a study that permitted patient access to the agent before market authorization.⁴ CONSIGN confirmed the safety profile of regorafenib, with no new safety signals. The most frequently reported regorafenibrelated treatment-emergent AEs of grade 3 or higher were hypertension (15%), hand-foot skin reaction (14%), fatigue (13%), diarrhea (5%), and hypophosphatemia (5%). REBECCA was a real-world cohort study nested within a compassionate use program.⁵ The most frequent AEs reported among patients in this cohort study were fatigue, hand-foot skin reaction, diarrhea, anorexia, arterial hypertension, and mucositis. Median OS was 5.6 months, and the 12-month OS rate was 22%. In CORRELATE, a real-world prospective, observational study of regorafenib in clinical practice, 24% of patients required a dose reduction because of a treatment-related AE.⁶ The most common grade 3/4 treatment-emergent AEs reported were fatigue (9%), hand-foot skin reaction (7%), and hypertension (6%). Median OS in this real-world study was 7.7 months (95% CI, 7.2-8.3), and median PFS was 2.9 months (95% CI, 2.8-3.0).

Since the original studies of regorafenib, much progress has been made in understanding how best to dose regorafenib. As was apparent in both the CORRECT and the CONCUR studies, AEs associated with regorafenib



Figure 2. SUNLIGHT: Overall survival (top) and progression-free survival (bottom) with trifluridine/tipiracil (FTD/TPI) ± bevacizumab. Adapted from Prager GW et al. *N Engl J Med.* 2023;388(18):1657-1667.¹⁴

tend to appear early, within the first 2 weeks of therapy. Additionally, a prolonged duration of regorafenib administration is important, given its action as a cytostatic agent. Therefore, optimizing the duration of therapy with regorafenib by successfully mitigating and preventing side effects is critical to improve patient outcomes.

This strategy was the underlying principle of the randomized phase 2 ReDOS trial.⁷ This study was designed to evaluate the effect of different regorafenib dosing regimens on the incidence and severity of regorafenibassociated toxicities as well as the effect on duration of therapy. Patients were randomized to treatment with either the standard dosing schedule (approved dose of 160 mg administered as 4 tablets once daily) or a doseescalation schedule in which patients began regorafenib treatment at half the approved dose per day in the first week (80 mg, administered as 2 tablets daily). In this latter arm, patients were then evaluated on a weekly basis to determine whether the dosage could be increased to 120 mg daily during week 2 and potentially up to the standard dose of 160 mg daily during week 3. After cycle 1, the dose during the second treatment cycle was determined on an individual basis as the dose that could be tolerated during the first cycle. In both the standard and the doseescalation arms, treatment was continued for 3 weeks, followed by 1 week off.

The results of the ReDOS study demonstrated that the primary endpoint, the likelihood that patients could proceed to cycle 3 after their post-cycle 2 scan, was significantly higher in the dose-escalation arm than in the standard dosing arm (43% vs 26%, 1-sided P=.043). Thus, approximately twice as many patients in the doseescalation arm were able to achieve at least stable disease after 2 cycles of regorafenib. This improved rate of disease control was thought to be a result of the longer duration of treatment in the dose-escalation arm. Importantly, the improved rates of stable disease achieved by patients in the dose-escalation arm translated to a trend of prolonged OS (median OS was 9.8 months in the dose-escalation arm vs 6.0 months in the standard dosing arm; Figure 1). However, this OS benefit did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank P=.12). Median PFS was similar in the 2 arms (2.8 months in the dose-escalation arm and 2.0 months in the standard dosing arm; HR, 0.84; 95% CI, 0.57-1.24; log-rank P=.38). The results of the ReDOS study were considered practice-changing and influenced in large measure how regorafenib is currently administered in the clinic.8

Trifluridine/Tipiracil With or Without Bevacizumab

Trifluridine/tipiracil is also FDA-approved in the treatment of refractory mCRC; it is indicated either as a single agent or in combination with bevacizumab for the treatment of adult patients who previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic therapy, and, if the tumor is RAS wild-type, an anti-EGFR therapy.⁹ Trifluridine/tipiracil is an antimetabolite oral combination formulation consisting of the thymidine-based nucleoside analogue trifluridine and the thymidine phosphorylase inhibitor tipiracil. The trifluridine is incorporated into the DNA, interfering with DNA synthesis and inhibiting cell proliferation, while the tipiracil increases trifluridine exposure by inhibiting thymidine phosphorylase-driven metabolism. The RECOURSE and TERRA clinical trials established the efficacy and safety of trifluridine/tipiracil in mCRC.

The RECOURSE study was a double-blind, randomized, phase 3 trial conducted to investigate the safety and efficacy of trifluridine/tipiracil in 800 patients with refractory mCRC.¹⁰ Patients were randomized to receive either trifluridine/tipiracil (35 mg/m² twice daily for 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period) or placebo, with best supportive care permitted in both arms. Treatment cycles were repeated up to 4 times. At randomization, patients were stratified by KRAS status, time from first diagnosis of metastasis, and geographic region. To be eligible, patients had to have received at least 2 prior standard treatments (including adjuvant chemotherapy). At baseline, the median patient age was 63 years, and 61% were male. ECOG performance status was 0 in 56% and 1 in 44%. Most patients (61%) had received 4 or more prior therapies.

Median OS, the primary endpoint of the RECOURSE study. was significantly prolonged in the trifluridine/tipiracil arm vs the placebo arm (7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58-0.81; P<.001). The improvement in OS achieved with trifluridine/tipiracil was observed across nearly all prespecified patient subgroups. A secondary endpoint, median PFS, was also significantly longer in the trifluridine/tipiracil arm (2.0 vs 1.7 months with placebo; HR, 0.48; 95% CI, 0.41-0.57; P<.001). As in the regoratenib trials, the overall response rate was low in both arms of the RECOURSE study (1.6% with trifluridine/tipiracil vs 0.4% with placebo; P=.29). The DCR, including patients with stable disease, was significantly higher with trifluridine/tipiracil than with placebo (44% vs 16%, respectively; P<.001). Patients treated with trifluridine/tipiracil also exhibited a significant delay in the worsening of their ECOG performance status from baseline levels of 0 or 1 to ≥ 2 (5.7 months with trifluridine/tipiracil vs 4.0 months with placebo; HR, 0.66; 95% CI, 0.56-0.78; P<.001).

The most common AEs associated with trifluridine/ tipiracil were related to myelosuppression and nausea. AEs of grade 3 or higher were more common with trifluridine/ tipiracil than with placebo, including neutropenia (38% vs 0%), anemia (18% vs 3%), and thrombocytopenia (5% vs <1%). In addition, nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%) of grade 3 or higher were more likely to develop in the trifluridine/ tipiracil arm than in the placebo arm.

The TERRA trial was a confirmatory, randomized, double-blind, placebo-controlled, phase 3 trial designed similarly to the RECOURSE study and planned to evaluate trifluridine/tipiracil in an Asian population.¹¹ Patients were randomized to treatment with trifluridine/tipiracil (n=271) or placebo (n=135). Patients in this Asian population had a lower overall exposure to biologic agents in prior lines of therapy.

The median OS, the primary endpoint of the TERRA trial, was 7.8 months with trifluridine/tipiracil vs 7.1 months with placebo. This difference was determined to be statistically significant (HR, 0.79; 95% CI, 0.62-0.99; log-rank P=.035). The incidence rates of serious AEs were similar in the 2 arms.

Given the modest response rates achieved with trifluridine/tipiracil, it was possible that its activity could be bolstered with a strategy of continuous inhibition of angiogenesis. The addition of the anti-VEGF agent bevacizumab to trifluridine/tipiracil was first explored in the phase 1/2 C-TASK FORCE study as well as in an investigator-initiated phase 2 trial.^{12,13} On the basis of promising initial results, the phase 3 SUNLIGHT trial was performed to compare the efficacy and safety of trifluridine/ tipiracil administered either alone or in combination with bevacizumab for the treatment of refractory mCRC.14

The SUNLIGHT trial enrolled adult patients with mCRC who had received no more than 2 prior lines of chemotherapy and who had experienced either disease progression or intolerable side effects with their most recent regimen. Prior treatments must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody, or an anti-EGFR monoclonal antibody (for patients with *RAS* wild-type disease). Prior treatments could have included neoadjuvant/adjuvant chemotherapy. Patients were required to have an ECOG performance status of 0 or 1.

Patients were randomized to receive trifluridine/ tipiracil either alone (n=246) or in combination with bevacizumab (n=246), all at their approved doses. Patients were stratified at the time of randomization according to geographic region (North America, European Union, or the rest of the world), time since diagnosis of the first metastasis (<18 vs ≥18 months), and RAS status (wildtype vs mutated). Baseline characteristics were balanced in the 2 treatment arms. The majority of patients (64.0%) were from the European Union, most (92.1%) had been treated with 2 prior lines of therapy, and 2.6% had received 3 or more prior regimens for mCRC. A total of 4.5% of patients in the trifluridine/tipiracil-plus-bevacizumab arm and 6.1% in the trifluridine/tipiracil-alone arm had received just one first-line triplet regimen. Time from diagnosis of first metastasis was 18 months or longer in 57.5% of the study population. Just under one-third of patients (30.7%) had RAS wild-type disease.

Median OS, the primary endpoint of the SUNLIGHT trial (Figure 2), was significantly longer in the trifluridine/ tipiracil-plus-bevacizumab arm than in the trifluridine/ tipiracil-alone arm (10.8 vs 7.5 months; HR, 0.61; 95% CI, 0.49-0.77; P<.001). The rates of 6-month OS (77% vs 61%) and 12-month OS (43% vs 30%) were both higher in the trifluridine/tipiracil-plus-bevacizumab arm than in the trifluridine/tipiracil-alone arm. Median PFS was also significantly prolonged in a comparison of trifluridine/tipiracil plus bevacizumab vs trifluridine/tipiracil alone (5.6 vs 2.4 months; HR, 0.44; 95%CI, 0.36-0.54; P<.001). The benefits in OS and PFS associated with trifluridine/ tipiracil plus bevacizumab were observed across multiple patient subgroups analyzed. The overall response rate was 6.1% in the trifluridine/tipiracil-plus-bevacizumab arm and was 1.2% in the trifluridine/tipiracil-alone arm. One patient achieved a complete response.

AEs of grade 3 or higher were reported in 72.4% of patients in the trifluridine/tipiracil-plus-bevacizumab arm and in 69.5% of patients in the trifluridine/tipiracilalone arm. The most commonly reported AEs in either group were neutropenia, nausea, and anemia. Patients treated with trifluridine/tipiracil plus bevacizumab more often experienced hypertension (10.2% vs 2.0% in the trifluridine/tipiracil-alone arm), nausea (37.0% vs 27.2%, respectively), and neutropenia (62.2% vs 51.2%, respectively), including grade 3 or higher neutropenia (43.1% vs 32.1%, respectively).

Fruquintinib

The most recently FDA-approved agent for the treatment of refractory mCRC is fruquintinib. This agent is indicated for the treatment of adult patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if the tumor is *RAS* wild-type and the treatment is medically appropriate, an anti-EGFR therapy.¹⁵ Fruquintinib is a novel, selective inhibitor of all VEGF1-3 receptors that has been shown to inhibit tumor growth and progression as well as lymphangiogenesis. Fruquintinib demonstrates limited off-target kinase activity, permitting a high level of drug exposure and sustained target inhibition. The efficacy and safety of fruquintinib were established in the FRESCO and FRESCO-2 trials.

FRESCO was a randomized, double-blind, placebocontrolled, multicenter phase 3 study conducted across China.¹⁶ Patients 18 to 75 years of age were eligible if they had confirmed mCRC that had progressed following at least 2 standard chemotherapy regimens and an ECOG performance status of 0 or 1. Patients were randomized in a 2:1 ratio to receive treatment with either 5 mg of fruquintinib (n=278) or placebo; treatment was administered orally once daily for 21 days, followed by 7 days off, in 28-day cycles until disease progression, intolerable toxicity, or study withdrawal.

The primary endpoint, median OS, was significantly prolonged with fruquintinib in comparison with placebo (9.30 vs 6.57 months; HR, 0.65; 95% CI, 0.51-0.83; log-rank test P<.001). Median PFS was also significantly prolonged with fruquintinib in comparison with placebo (3.71 vs 1.84 months; HR, 0.26; 95% CI, 0.21-0.34; P<.001). The overall response rate was higher with fruquintinib than with placebo (4.7% vs 0%; P=.01; treatment difference, 4.7% [95% CI, 2.1%-7.2%]), as was the DCR including stable disease (62.2% vs 12.3%; P<.001; treatment difference, 49.9% [95% CI, 42.0%-57.8%]). One patient in the fruquintinib arm achieved a complete response.

Treatment-emergent grade 3/4 AEs occurred in 61.2% of the fruquintinib arm and 19.7% of the placebo arm. The most common grade 3/4 AEs reported with fruquintinib were hypertension (21.2%), hand-foot skin reaction (10.8%), and proteinuria (3.2%). Serious AEs also were more frequent with fruquintinib than with placebo (15.5% vs 5.8%), and a higher percentage of



Figure 3. FRESCO-2: Overall survival in patients treated with fruquintinib vs placebo. HR, hazard ratio. Adapted from Dasari A et al. *Lancet.* 2023;402(10395):41-53.¹⁷

patients in the fruquintinib arm required hospitalization (14.4% vs 5.1% in the placebo arm).

FRESCO-2 was an international, randomized, doubleblind, placebo-controlled phase 3 trial that was conducted at 124 sites across 14 countries throughout North America, Europe, Asia, and Australia.¹⁷ Patients were eligible if they were 18 years of age or older (\geq 20 years in Japan); had an ECOG performance status of 0 or 1; had received all standard treatments, including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if the tumor was *RAS* wild-type); and had disease progression on or had been unable to tolerate either regorafenib or trifluridine/tipiracil.

Patients were randomized to receive either 5 mg of fruquintinib or matched placebo orally once daily on days 1 through 21 of 28-day cycles. Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, discontinuation by the physician, or study completion or termination. Best supportive care was permitted in both arms.

The primary endpoint of OS was significantly longer in the fruquintinib arm than in the placebo arm (median OS, 7.4 vs 4.8 months; HR, 0.66; 95% CI, 0.55-0.80; P<.0001). The Kaplan-Meier analysis (Figure 3) demonstrated an early separation of the curves, indicating early benefit with fruquintinib that was maintained over the duration of the study. Median PFS, a secondary endpoint, was also significantly improved with fruquintinib vs placebo (3.7 vs 1.8 months; HR, 0.32; 95% CI, 0.27-0.39; *P*<.0001). The overall response rate was 2% with fruquintinib and 0% with placebo; no complete responses were observed. The DCR, including stable disease, was 56% with fruquintinib and 16% with placebo (adjusted difference, 39%; 95% CI, 32.8%-46.0%; *P*<.0001).

AEs of grade 3 or higher were reported in 63% of the fruquintinib arm and in 50% of the placebo arm. The most frequent AEs of grade 3 or higher with fruquintinib were hypertension (14%), asthenia (8%), and hand-foot syndrome (6%).

Disclosure

Dr Barzi has received consulting fees from Bayer and Astra-Zeneca.

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Real-World Data on Sequencing Third-Line Therapies for Metastatic Colorectal Cancer

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uidelines for the treatment of refractory mCRC do not include recommendations on the sequencing of FDA-approved third-line therapies for mCRC. In the absence of head-to-head trials, we now must turn to emerging data from real-world clinical practice to provide insight into optimal sequencing strategies for these agents.

Regorafenib vs Trifluridine/Tipiracil

A nationwide health record–derived, de-identified Flatiron Health database, which included data from more than 280 US cancer clinics comprising primarily community practices, was used to provide patient data for a comparison of the real-world use of regorafenib vs that of trifluridine/ tipiracil.¹ Patients in whom mCRC was diagnosed between 2015 and 2020 and who had received a minimum of 2 lines of standard fluorouracil-based chemotherapy, followed by treatment with either regorafenib or trifluridine/tipiracil, were included in this analysis. Both Kaplan-Meier and propensity score–weighted proportional hazards models were applied to compare the survival rates of patients who had received either treatment.

Patients were classified as having received trifluridine/tipiracil alone or before regorafenib (n=921) or as having received regorafenib alone or before trifluridine/ tipiracil (n=1016). The median OS among patients in the trifluridine/tipiracil group was 6.66 months, which was similar to the median OS of 6.30 months among patients in the regorafenib group. No significant differences in survival were observed in an exploratory subgroup analysis of patients stratified by age, performance status, *RAS/RAF*



Figure 4. STAR-T: Overall survival (OS) with regorafenib followed by trifluridine/tipiracil ± bevacizumab (R-T) and with trifluridine/tipiracil ± bevacizumab followed by regorafenib (T-R) in the fourth-line setting. HR, hazard ratio; IQR, interquartile range; KM, Kaplan-Meier. Adapted from Nevala-Plagemann C et al. *J Natl Compr Canc Netw.* 2023;21(3):257-264.¹

*Adjusted for age, sex, ECOG performance status, *KRAS* mutation status, prior targeted treatments (anti-EGFR or bevacizumab), and stage at initial diagnosis.

status, microsatellite instability status, tumor sidedness, or prior targeted therapy received.

This large real-world comparison of regorafenib and trifluridine/tipiracil in the third-line setting revealed relatively equal use of the 2 agents following their approval and also showed no significant difference in the OS of patients who received treatment with either agent in the third-line setting.

The STAR-T Study

STAR-T was a retrospective cohort study that followed patients from January 2015 to February 2023.² The goal of STAR-T was to assess the characteristics and clinical outcomes of patients with mCRC who were treated sequentially under real-world conditions with either regorafenib followed by trifluridine/tipiracil ± bevacizumab (R-T) or the opposite sequence of trifluridine/tipiracil ± bevacizumab followed by regorafenib (T-R). A total of 818 patients were selected from the Flatiron Health database previously described.

After receiving their first treatment in the sequence (referred to as the index treatment), patients were followed

for a minimum of 3 months or until death, last date of activity, or study completion. To be eligible for enrollment, patients had to be 18 years of age or older at the time of their mCRC diagnosis. Patients with a gastrointestinal stromal tumor, hepatocellular carcinoma, or another primary cancer diagnosis (except nonmelanoma skin cancers) in the 6 months before they received their index treatment were excluded from enrollment.

The baseline characteristics were largely similar in the 2 treatment groups. The median age in both groups was 63 years; 59% (R-T) and 53% (T-R) were male. At the time of their diagnosis, most patients had stage IV disease (55% in the R-T group and 56% in the T-R group). The median time since diagnosis was approximately 24.5 months in both groups. The majority of patients had an ECOG performance status of 0 or 1 (71% in both groups); 8% in the R-T group and 10% in the T-R group had an ECOG performance status of 2 or higher. A *KRAS* mutation was present in 47% of the R-T group and 46% of the T-R group, and a *BRAF* mutation was present in 1% and 4%, respectively. Most patients received their index treatment as third-line (42% in the R-T group and 41% in



Figure 5. OSERO: Overall survival with different sequences: regorafenib first (REG), trifluridine/tipiracil + bevacizumab first (FTD/TPI+BEV), and trifluridine/tipiracil alone first (FTD/TPI). Adapted from Bekaii-Saab T et al. *Ann Oncol.* 2023;34(suppl 2):S410-S457.²

the T-R group) or fourth-line (22% in the R-T group and 25% in the T-R group) therapy. A subset of the patients was treated in the fifth line (12% in the R-T group and 11% in the T-R group). Approximately one-third of the patients had received a prior anti-EGFR therapy (33% in the R-T group and 36% in the T-R group), and most had received prior bevacizumab (78% in the R-T group and 79% in the T-R group). A total of 11% in the R-T group and 15% in the T-R group had received prior trifluridine/ tipiracil plus bevacizumab.

Overall, a trend toward longer OS was observed with the R-T sequence vs the T-R sequence, although the difference did not achieve statistical significance. For example, among the patients who received their index treatment in the third-line setting, the median OS was 13.1 months with R-T vs 11.5 months with T-R (adjusted HR, 0.99; 95% CI, 0.75-1.29). Similarly, in the patients who received their index treatment in the fourth-line setting (Figure 4), the median OS was 11.6 months with R-T vs 10.3 months with T-R (adjusted HR, 0.90; 95% CI, 0.61-1.31).

The Kaplan-Meier estimated median times to discontinuation of the sequential therapy were 8.7 and 8.5 months for the R-T group in the third-line and fourth-line settings, respectively. By comparison, the median times to discontinuation of the sequential therapy were 8.1 and 7.9 months, respectively, for the T-R group. Although the times to discontinuation of sequential therapy were slightly longer with R-T than with T-R in both the thirdand fourth-line settings, the differences were not statistically different. Similar proportions of patients in the 2 groups went on to receive subsequent therapy (34% in the R-T group and 35% in the T-R group).

The frequencies of moderate or severe neutropenia were numerically lower in the R-T group (26% and 12%, respectively) than in the T-R group (32% and 16%, respectively). Overall, slightly fewer patients in the R-T group received granulocyte colony-stimulating factor (G-CSF) during the study period (14% in the R-T group vs 18% in the T-R group). The incidence rate for G-CSF was 14.9 per 1000 person-months in the R-T group and 22.2 per 1000 person-months in the T-R group.

These results, although not achieving statistical significance, together suggest that there may be a benefit with the sequential use of regorafenib followed by trifluridine/ tipiracil ± bevacizumab. In particular, this sequence allows patients to have a chemotherapy-free break after receiving 2 or more initial lines of cytotoxic chemotherapy and before continuing to treatment with trifluridine/tipiracil ± bevacizumab in a later line.

The OSERO Study

Presented at the 2024 ASCO Gastrointestinal Cancers Symposium, the OSERO study was a prospective observational study that also evaluated the effect of the sequence of these agents on OS.3 The study enrolled patients with mCRC from 42 sites across Japan. Key inclusion criteria included that the patient have an ECOG performance status of 0 or 1, have had no prior treatment with either regorafenib or trifluridine/tipiracil, and be considered refractory to or intolerant of standard therapy (fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF(R) monoclonal antibody, and anti-EGFR monoclonal antibody [if the tumor was RAS wild-type]). A total of 149 patients received regorafenib first (index treatment), followed by trifluridine/tipiracil ± bevacizumab; 80 patients received trifluridine/tipiracil first followed by regorafenib; and 226 patients received trifluridine/tipiracil + bevacizumab first followed by regorafenib. Although patients planned for their sequential therapy, its selection was not mandatory.

The median OS among patients who received regorafenib as the index treatment was 11.8 months, which was significantly longer than the OS of 7.1 months noted in the patients who received trifluridine/tipiracil alone as the index treatment (HR, 0.72; 95% CI, 0.52-0.99; P=.043). The median OS for patients treated with trifluridine/tipiracil + bevacizumab as the index treatment was 10.3 months, which was not significantly different from the median OS for the regorafenib group (HR, 1.03; 95% CI, 0.79-1.33; P=.828). Figure 5 shows the OS analysis for the 3 groups in this study. These data provide further evidence, in addition to the STAR-T study, for improved survival when regorafenib is used first in the sequence, followed by trifluridine/tipiracil ± bevacizumab.

Real-World Adherence

With the use of data from the US IQVIA Real-World & Health Data Sets, a retrospective longitudinal cohort study was conducted to assess real-world treatment patterns and the adherence of patients with mCRC who were treated with regorafenib or trifluridine/tipiracil, and also to explore the effect of treatment sequencing on adherence patterns.⁴ A total of 780 patients were included in this analysis. The mean duration of treatment was significantly longer in the patients who received trifluridine/tipiracil than in those who received regorafenib (94 vs 81 days; *P*<.001).

Among this group of patients, the mean medication possession ratio (MPR), a measure of medication adherence, was significantly higher for patients receiving trifluridine/tipiracil than for patients receiving regorafenib (0.93 vs 0.86; P<.001); patients with an MPR higher than 0.80 were considered adherent to their therapy. The percentage of patients with an MPR of 0.80 or higher was higher with trifluridine/tipiracil than with regorafenib (87.1% vs 72.6%; P<.001), as was the percentage of patients with an MPR of 0.90 or higher (74.6% vs 54.3%; P<.001).

Proportion of days covered (PDC) was defined as the number of unique days with medication divided by the length of a fixed time interval. This second measure of adherence showed similar results, with the mean PDCs at 3 and 6 months significantly higher among the patients treated with trifluridine/tipiracil than among those treated with regorafenib (mean 3-month PDC, 0.72 vs 0.60; *P*<.001; mean 6-month PDC, 0.56 vs 0.48; *P*=.020).

In this data set, patients who switched from trifluridine/tipiracil to regorafenib (n=96) and patients who switched from regorafenib to trifluridine/tipiracil-(n=83) were identified for a subgroup analysis. The proportion of patients considered to be adherent (MPR ≥ 0.80) was significantly higher in the group that switched from trifluridine/tipiracil to regorafenib than in the group that switched from regorafenib to trifluridine/tipiracil (79.2% vs 57.8%; *P*=.002; odds ratio, 2.91; *P*=.004). Further, patients who switched from trifluridine/tipiracil to regorafenib had a longer mean duration of first treatment in comparison with patients who switched from regorafenib to trifluridine/tipiracil (102 vs 82 days; *P*=.002).

These real-world data suggest that rates of adherence were higher with trifluridine/tipiracil than with regorafenib, and rates of treatment discontinuation were lower. Furthermore, adherence and persistence were higher in the patients who switched from trifluridine/ tipiracil to regorafenib than in those who switched from regorafenib to trifluridine/tipiracil.

Disclosure

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Sequencing Third-Line Therapies for Metastatic Colorectal Cancer: A Guide for Determining Which Therapy to Use First

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Treatment Guidelines

urrent guidelines from the National Comprehensive Cancer Network (NCCN) place equal weight on the use of regorafenib, trifluridine/ tipiracil, and fruquintinib for the treatment of mCRC that has progressed though all available systemic therapy regimens (Table).¹ The guidelines do note that regorafenib has shown activity only in patients whose disease has progressed on all standard therapy, and thus the NCCN Panel added regorafenib as another line of therapy for patients with mCRC refractory to chemotherapy. Similarly, the NCCN Panel added trifluridine/ tipiracil, with or without bevacizumab, as a treatment option for patients whose mCRC has progressed through standard therapies, noting that trifluridine/tipiracil plus bevacizumab was preferred to trifluridine/tipiracil alone. The NCCN Panel also recommended fruquintinib as a treatment option for mCRC that has progressed through all other available regimens. For all 3 agents, the NCCN guidelines state that each can be given before or after the other 2 agents, in the absence of data to inform the best order of these therapies.

Sequencing Considerations

In general, the sequencing of treatments in mCRC

is one of those matters about which we do not have a tremendous amount of knowledge. Even in earlier lines of therapy, the actual sequencing (which backbone chemotherapy should go first, what type of biologic agent should follow, and in what order should they be used?) remains controversial. Despite accumulating evidence that left-sided tumors respond better to EGFR inhibitors in the frontline,² a large use of non-EGFR therapies for left-sided tumors continues in the community; this practice can likely be attributed to the earlier development of antiangiogenic therapies and their availability before the anti-EGFR inhibitors.

When we look at the way we are currently sequencing these drugs, several questions come to mind: which one should we use first, in what order should we use them, and can we continue to rechallenge with subsequent chemotherapies? Most of the studies that have focused on rechallenge of chemotherapies, unless the drug was administered at a very early stage of disease and was discontinued electively and not for toxicity or progression, have shown very little benefit. With regorafenib, at least real-world data have shown much better survival than what we would get if we were to rechallenge with chemotherapy.

Most patients enter the refractory mCRC setting about 1.5 to 2 years after the time of initial diagnosis. These patients have been through significant combination chemotherapy (FOLFOX and FOLFIRI), and they have
 Table.
 Systemic Therapy for Metastatic Colorectal Cancer That

 Has Progressed Through All Available Regimens
 Progressed Through All Available Regimens

Fruquintinib

Fruquintinib 5 mg orally daily on days 1-21 Repeat every 28 days

Regorafenib

Regorafenib 160 mg orally daily on days 1-21 or First cycle: regorafenib 80 mg orally daily on days 1-7,

followed by 120 mg orally daily on days 8-14, followed by 160 mg orally daily on days 15-21

Subsequent cycles: regorafenib 160 mg orally daily on days 1-21

Repeat every 28 days

Trifluridine + tipiracil ± bevacizumab

Trifluridine + tipiracil 35 mg/m² up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily on days 1-5 and 8-12 Bevacizumab 5 mg/kg on days 1 and 15 Repeat every 28 days

Adapted from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines*). Colon cancer. Version 2.2024.¹

endured the toxic effects of cytotoxic chemotherapies, such as cytopenia and mucositis. Thus, many patients by this point are looking for ways to get a break from these side effects. Agents such as regorafenib and fruquintinib provide a chemotherapy break for this patient population, essentially opening the door to treatment with agents that have a different toxicity profile.

For an example, consider a case of right-sided mCRC treated with frontline chemotherapy (any backbone) plus an antiangiogenic agent and in the second-line with an anti-EGFR agent (either cetuximab or panitumumab) because the tumor is right-sided. If that patient has experienced a tremendous amount of skin rash or other skin toxicity, I may hold off on using regorafenib immediately in the third line. For that patient, I might instead use trifluridine/tipiracil to provide a little bit of a break from the skin toxicity. However, one must remain mindful that a patient just coming off chemotherapy may already have low blood cell counts that could be further aggravated by the myelosuppression associated with trifluridine/ tipiracil. In contrast, for a patient who has a RAS-mutant tumor, cetuximab may never be used, and that patient's skin will essentially be untouched by toxicities. In these cases, I tend to move on to regorafenib immediately at the moment of progression after the second line of therapy, using a dose-escalation strategy to spare the patient as much skin toxicity as possible and prolong the duration of therapy.

It is also important to consider what factors are important to each patient. For example, these patients have been coming to the infusion unit every 2 weeks for their therapies until this point. Perhaps we can think about giving them oral therapies to allow them freedom from clinic time or freedom from infusion time. And now, with the availability of telehealth for patient follow-up, it perhaps gives them more time at home, which is what we all want. So, those are the considerations to keep in mind.

Patient and Tumor Characteristics Driving Treatment Decisions

Other variables should be considered as well. For example, how did the patient respond to prior therapies? Some of these patients may have had remarkable responses with prior therapies. Much discussion has recently centered on whether one drug might be more active than another in the setting of extrahepatic disease. However, we do not yet have evidence to say that liver metastasis will be a determining factor in response to any particular agent. In the original studies of regorafenib, it was seen that the patients who had mostly lung metastases in which cavitation developed tended to have a longer OS. Does that mean that patients with lung metastases are more sensitive to the regorafenib? This remains to be proven. Similarly, in the clinical trials of trifluridine/tipiracil, the patients in whom the most profound neutropenia developed tended to have the best OS. Again, it remains unproven whether this means that these patients were more sensitive to trifluridine/tipiracil.

The truth is that there is no biological determining characteristic that will tell me, "Use this medication before the other one," because all patients were eligible, and all patients derived benefit. Looking at the hazard ratios and the subgroup analyses from the pivotal clinical trials, the benefits were seen across all patient subgroups. Unlike with other gastrointestinal cancers, such as pancreatic or gastric cancers, what I have seen in my clinical practice with mCRC is that the rate of dropout among patients who cannot tolerate subsequent lines of therapy is no more than 10% to 15% per line of therapy, so that by the third line, 70% to 80% of my patients are still able to proceed to their next line of therapy. The fourth line will still be relevant for 60% to 70% of the population. For these reasons, we believe that all patients should be offered the medications at one point during their disease.

Introducing Regorafenib Earlier in Treatment

The REVERCE study suggested that it might be even better to use regorafenib earlier than the third line. The REVERCE trial was an open-label, randomized, phase 2 trial in Japan that compared the sequence of regorafenib followed by cetuximab (n=51) with the reverse sequence of cetuximab followed by regorafenib (n=50).³ In both arms, cetuximab could be administered with or without irinotecan. The study was stopped prematurely because of slow enrollment and a lack of funding, but it did demonstrate a statistically significant benefit in the primary endpoint of OS with the sequence of cetuximab followed by regorafenib followed by regorafenib followed by regorafenib (median OS of 17.4 vs 11.6 months, respectively; HR, 0.61; 95% CI, 0.39-0.96; P=.0293).

The main issue with using regorafenib earlier is the toxicities that can occur, and this problem has certainly been what has caused clinicians to be cognizant of when to use the medication. However, we have seen that if the patients are treated with the dose-escalation strategy for regorafenib, tolerance tends to be much better and the duration of treatment longer, and overall, they tend to be on the medication for a longer time.

Disclosure

Dr Cusnir is a speaker for Guardant Health.

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How Best to Extend Overall Survival in Metastatic Colorectal Cancer: Q&A

Tanios S. Bekaii-Saab, MD, Afsaneh Barzi, MD, PhD, and Mike Cusnir, MD

Tanios S. Bekaii-Saab, MD What are the early signs of progression in the second line that may cause the physician to move the patient earlier to one of the third-line therapies?

Mike Cusnir, MD The possibility of moving the patient from a line of therapy should be considered when any new lesions are identified. It is important to remember that according to RECIST criteria, the appearance of a new lesion is already considered disease progression. Currently, most oncologists monitor patients with computed tomography every 2 to 3 months, which is longer than the monthly scans that used to be done, so they must be diligent about identifying whether a patient fits the criteria for disease progression with more than a 20% increase in the index lesions or the appearance of new lesions. Another consideration should be the appearance of any type of toxicity that is causing patient intolerance to the current medication. Any of these signs of progression signal the need to move immediately to the next lines of therapy. It is critical to move quickly, before losing the functional capacity of the patient, to be able to continue with the other lines of therapy.

Tanios S. Bekaii-Saab, MD What other recommendations do you have for sequencing when a patient is transitioning from second line to third line, or for shifting the mindset from focusing on the response rate to focusing on disease control?

Mike Cusnir, MD The focus needs to be on a prompt transition, so as soon as the patient is showing signs of progression (weight loss, some decline in the overall performance status, or even just worsening pain), the oncologist must already be moving to the next medications. Because insurance delays tend to be common when these medications are requested, oncologists need to be proactive when they see early signs of progression and start the process of obtaining insurance approval for the subsequent line of therapy.

Regarding the second part of the question, I always tell my patients that I will take a cancer that does not grow any day of the week, that stable disease is actually great in the setting of refractory mCRC. Although we certainly want to see shrinkage, with tumors decreasing in size, the measure of depth of response in the third-line setting—that is, how much the size of the tumor decreases in

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]). Colon cancer. Version 2.2024. April 30, 2024. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 7, 2024.

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comparison with what it was before—is essentially meaningless. However, tumor stability is meaningful and translatable to a survival benefit. I have in my clinic patients with refractory mCRC who have had stable disease for more than a year. The tumors are there, but we need to be mindful that stable disease indicates disease control, and that is a goal that we are aiming for.

Afsaneh Barzi, MD, PhD Nearly all patients in the refractory setting have been through essentially 2 years of mostly combination cytotoxic chemotherapy, and many have endured toxicities such as cytopenia and mucositis and are looking for ways to get away from those side effects. Regorafenib and fruquintinib may provide an advantage for this patient population because the agents have a different toxicity profile, which could alleviate some of the treatment burden associated with cytotoxic chemotherapy.

For a minority of patients, such as those with *BRAF* mutation, who have the targeted therapy options minus the cytotoxic agents, at least for second-line therapy, tri-fluridine/tipiracil + bevacizumab may be the right way to move forward because that is when cytotoxic therapy can be reintroduced, as opposed to going with the targeted therapies.

Another consideration to keep in mind is what is important to the patient. These patients have been coming to the infusion unit every 2 weeks up to this point, so perhaps a review of therapies to give them freedom from clinic or infusion time is appropriate. With oral agents—regorafenib, fruquintinib, and trifluridine/ tipiracil alone—patients do not need to come in for an infusion. With the availability of telehealth, they will have more time at home.

Other important variables I consider are how patients did with prior therapies, the site of disease, and the extent of disease (involvement of other organs or lymph nodes). Obviously, the refractory space is challenging. Patients in this setting need close monitoring and follow-up. They can deteriorate quickly from both the aspects of their disease and the side effects of therapy. In terms of our ability to deliver these agents and when thinking about how to bring a different agent into the place, it is critical to create and maintain a close relationship with patients and help them understand the importance of contacting us if they experience something new. Working with patients closely to maintain their performance status and their viability, so that these agents can be used one after another, is a key factor in this decision-making.

Tanios S. Bekaii-Saab, MD What will be the treatment strategies to extend overall survival in the future?

Mike Cusnir, MD I expect that there will be more combinations and that at some point the currently approved medications will be used with better biomarker sequencing for a small subgroup of patients. We hope such developments will result in better response criteria (for example, circulating tumor DNA) or improved analysis of imaging studies, or it might be just that completely different biomarkers will be used to confirm that the drug is doing what is needed.

Slide Library

Treatment of Refractory mCRC

- The treatment of refractory mCRC has seen significant growth over the past decade
- There are 3 primary treatments approved by the US Food and Drug Administration for use in the third-line setting: regorafenib, trifluridine/tipiracil with or without bevacizumab, and fruguintinib
- Common among these agents is the targeting of the VEGF pathway

mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor.

Regorafenib

- Considered a chemotherapy-free approach to treat mCRC, regorafenib is a small-molecule inhibitor of multiple kinases
- The efficacy and safety of regorafenib in the third-line setting were established in 2 clinical trials: CORRECT and CONCUR
- CONSIGN confirmed the safety profile of regorafenib, with no new safety signals. Treatment-emergent AEs of grade 3 or higher were hypertension (15%), hand-foot skin reaction (14%), fatigue (13%), diarrhea (5%), and hypophosphatemia (5%)¹
- In the ReDOS study, improved rates of stable disease achieved by patients in the dose-escalation arm translated to a trend of prolonged OS (median OS was 9.8 months in the dose-escalation arm vs 6.0 months in the standard dosing arm)²
- AEs, adverse events; OS, overall survival. 1. Van Cutsem E et al. Oncologist. 2019;24(2):185-192; 2. Bekaii-Saab TS et al. Lancet Oncol. 2019;20(8):1070-1082.

Trifluridine/Tipiracil With or Without Bevacizumab

- The RECOURSE and TERRA clinical trials established the efficacy and safety of trifluridine/tipiracil in mCRC
- Median OS, the primary endpoint of the RECOURSE study, was significantly prolonged in the trifluridine/tipiracil arm vs the placebo arm (7.1 vs 5.3 months)¹
- The most common AEs associated with trifluridine/tipiracil were related to myelosuppression and nausea
- Median OS, the primary endpoint of the SUNLIGHT trial, was significantly longer in the trifluridine/tipiracil-plus-bevacizumab arm than in the trifluridine/tipiracil-alone arm (10.8 vs 7.5 months)²

1. Mayer RJ et al. N Engl J Med. 2015;372(20):1909-1919; 2. Prager GW et al. N Engl J Med. 2023;388(18):1657-1667.

Fruquintinib

- Fruquintinib is a novel, selective inhibitor of all VEGF1-3 receptors that has been shown to inhibit tumor growth and progression as well as lymphangiogenesis
- The efficacy and safety of fruquintinib were established in the FRESCO and FRESCO-2 trials
- In FRESCO, the primary endpoint, median OS, was significantly prolonged with fruquintinib vs placebo (9.30 vs 6.57 months)¹
- The most common treatment-emergent grade 3/4 AEs occurring in 61.2% of the fruquintinib arm and 19.7% of the placebo arm were hypertension (21.2%), hand-foot skin reaction (10.8%), and proteinuria (3.2%)¹
 - 1. Li J et al. JAMA. 2018;319(24):2486-2496.

Regorafenib vs Trifluridine/Tipiracil

- A nationwide health record-derived de-identified Flatiron Health database was used to provide patient data for a comparison of realworld use of regorafenib vs trifluridine/tipiracil¹
- The median OS among patients in the trifluridine/tipiracil group was 6.66 months, similar to the median OS of 6.30 months among patients in the regorafenib group
- The large real-world comparison of regorafenib and trifluridine/tipiracil in the third-line setting revealed relatively equal use of both agents since their approvals, and showed no significant difference in the OS of patients who were treated with either agent in the third-line

1. Nevala-Plagemann C et al. J Natl Compr Canc Netw. 2023;21(3):257-264.

The STAR-T and OSERO Studies

- The goal of STAR-T was to assess the characteristics and clinical outcomes of patients with mCRC who were treated sequentially under real-world conditions, with either R-T or the opposite sequence of T-R¹
- * A trend towards longer OS was observed with the R-T sequence vs the T-R sequence, although not statistically significant
- Frequencies of moderate or severe neutropenia were numerically lower in the R-T group compared with the T-R group
- * The OSERO study data provide further evidence, in addition to the STAR-T study, for improved survival when regorafenib is used first in the sequence, followed by trifluridine/tipiracil ± bevacizumab²
- R-T, regorafenib followed by trifluridine/tipiracil ± bevacizumab; T-R, trifluridine/tipiracil ± bevacizumab followed by regorafenib. 1. Bekaii-Saab T et al. *Ann Oncol.* 2023;34(suppl 2):S410 S457; 2. Chida A et al. *J Clin Oncol.* 2024;42(suppl 3). Abstract 103.

Real-World Adherence

- A retrospective longitudinal cohort study was conducted to assess real-world treatment patterns and adherence of patients with mCRC who were treated with regorafenib or trifluridine/tipiracil
- The mean MPR, a measure of medication adherence, was significantly higher for patients receiving trifluridine/tipiracil vs patients receiving regorafenib
- In a subgroup analysis, the proportion of patients considered to be adherent (MPR ≥0.80) was significantly higher in the group who switched from trifluridine/tipiracil to regorafenib compared with the group who switched from regorafenib to trifluridine/tipiracil

MPR, medication possession ratio.

Sequencing Considerations

- Current NCCN guidelines place equal weight on the use of regorafenib, trifluridine/tipiracil, and fruquintinib for the treatment of mCRC that has progressed though all available systemic therapy regimens
- Even with evidence building up of left-sided tumors responding better to EGFR inhibitors in the frontline,¹ there is still a large use in the community of non-EGFR therapies in left-sided tumors
- Agents such as regorafenib and fruquintinib provide a chemotherapy break for the refractory mCRC patient population, essentially opening the door to treating these patients with agents with a different toxicity profile

1. Yoshino T et al. J Clin Oncol. 2022;40:LBA1-1

Patient and Tumor Characteristics Driving Treatment Decisions

- Variables to consider include how the patient responded to prior therapies
- In the original studies of regorafenib, it was seen that the patients who had mostly lung metastases that developed cavitation tended to have longer OS. Whether patients with lung metastases have more sensitivity to the regorafenib remains to be proven
- Similarly, in the clinical trials of trifluridine/tipiracil, the patients who developed the most profound neutropenia tended to have the best OS. Again, it remains unproven whether these patients were more sensitive to trifluridine/tipiracil

Introducing Regorafenib Earlier in Treatment

- The REVERCE study suggested that it might be even better to use
 regorafenib earlier than the third line
- The REVERCE study was stopped prematurely owing to slow enrollment and a lack of funding but did demonstrate a statistically significant benefit in the primary endpoint of OS with the sequence of regorafenib followed by cetuximab vs the sequence of cetuximab followed by regorafenib (median OS of 17.4 vs 11.6 months, respectively)
- The main issue with using regorafenib earlier is the toxicities that can
 occur, and this has caused clinicians to be cognizant of when to use
 the medication. However, when refractory mCRC patients are treated
 with the dose-escalating strategy for regorafenib, tolerance tends to
 be better, duration of treatment is longer, and they stay on the
 medication for a longer time

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