Abstract: Until recently, treatment options for patients with metastatic colorectal cancer (CRC) were limited to chemotherapy, vascular endothelial growth factor–targeted therapy, and, for patients with RAS-wild type tumors, epidermal growth factor receptor–targeted therapy. For patients with disease progression after treatment, newer agents are now available: the multitargeted tyrosine kinase inhibitor regorafenib and the cytotoxic combination of trifluridine and tipiracil (TAS-102). Both regorafenib and trifluridine/tipiracil have demonstrated significant improvements in overall survival in patients with refractory metastatic CRC. Durable responses exceeding a year have been reported with regorafenib. The agents differ in their safety profiles. Regorafenib is associated with hand-foot skin reaction and fatigue, primarily in the first cycle. Alternative dosing strategies appear to improve the tolerability of regorafenib, and randomized dosing studies are underway to define the optimal strategy. Trifluridine/tipiracil is associated primarily with myelosuppression. Sequencing of these agents can be guided by patient characteristics, such as comorbidities and adverse reactions to previous treatments. Patients with a poor performance status are not likely to benefit from regorafenib. Ongoing studies are further defining the role of regorafenib and trifluridine/tipiracil in the treatment of metastatic CRC.
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Colorectal cancer (CRC) is a common disease, diagnosed in nearly 1.4 million people worldwide annually.¹ In the United States, there are nearly 133,000 new diagnoses each year.² Approximately one-third of patients with CRC will develop metastatic disease. In most of these patients, the disease relapses and becomes refractory.

Most cases of CRC arise spontaneously. However, there are some well-recognized and characterized genetic predispositions. Inherited syndromes, such as Lynch syndrome (hereditary nonpolyposis colorectal cancer) and familial polyposis, increase the risk. Lifestyle issues also play a significant role. Environmental factors, including diet and exercise, are receiving increasing attention, as is the potential role of fecal flora.

The overall prognosis of patients with metastatic CRC has improved significantly in the past several decades. Twenty-five years ago, average survival was less than a year, compared with 30 months today.³ New research has identified different molecular subtypes of CRC. A greater understanding of these subtypes will likely lead to further improvements in the treatment of CRC. Although some patients with metastatic CRC can be cured through surgical and ablative techniques, the disease remains incurable in most cases. There is clearly a need for new therapeutic approaches.

### Recent Clinical Trials in Relapsed/Refractory Metastatic Colorectal Cancer

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Early Treatment of Relapsed/Refractory Metastatic CRC

The initial treatment of relapsed/refractory metastatic CRC typically involves combination chemotherapy, often consisting of fluorouracil (5-FU), irinotecan, and oxaliplatin plus a biologic agent. In the United States, the most common biologic agent in this regimen is the vascular endothelial growth factor (VEGF) inhibitor bevacizumab. Unfortunately, most patients will relapse after initial therapy or develop progressive disease during first-line treatment. Therefore, subsequent therapies are often needed.

Many active agents are available for the treatment of metastatic CRC. The goal of treatment algorithms is to expose patients to all appropriate therapies. Selection of therapies has been enhanced with the advent of molecular profiling. All patients should be tested for RAS (KRAS and NRAS), BRAF, and microsatellite instable (MSI)/microsatellite stable (MSS) mutations. Approximately 40% of patients lack RAS and BRAF mutations and are categorized as RAS/BRAF-wild type.⁴ Epidermal growth factor receptor (EGFR) monoclonal antibodies, such as panitumumab or cetuximab, are likely to be effective only in these patients.⁵ For patients with RAS mutations, EGFR monoclonal antibodies are ineffective, and may in fact be harmful.⁶

EGFR monoclonal antibodies are often used in the second-line setting after first-line treatment with VEGF inhibitors. They appear to be similarly effective regardless of the line of therapy in which they are used.⁷ Though some clinicians reserve EGFR inhibitors for third-line therapy, primarily because of the associated adverse events, including a potentially severe rash.⁸ Another option is to use anti-EGFR therapy in the frontline setting, moving VEGF inhibitors to second- and third-line treatment.

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With Regorafenib or Placebo After Failure of Standard Therapy) trial, an international, multicenter, randomized, phase 3 trial that enrolled 760 patients with refractory metastatic CRC.\textsuperscript{17} Patients had refractory disease and a good performance status. Any RAS mutation status was allowed. Patients were assigned 2:1 to regorafenib at 160 mg/day or placebo once daily for the first 3 weeks of each 4-week cycle, plus best supportive care.

The primary endpoint, overall survival, was met. Regorafenib demonstrated a significant improvement in median overall survival over placebo (6.4 months vs 5.0 months, respectively; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; 1-sided \( P = .0052 \); Figure 1). Regorafenib was also associated with an improvement in progression-free survival (PFS) over placebo, with a median PFS of 1.9 months vs 1.7 months, respectively (HR, 0.49; 95% CI, 0.42-0.58; \( P < .0001 \); Figure 2). Although the average survival benefit associated with regorafenib was relatively short at 1.4 months, some patients had a clear benefit for a prolonged period of time. As many as 20% of patients had stable disease for 6 months or longer. Although the Response Evaluation Criteria In Solid Tumors (RECIST) response rate was essentially 0, some patients did have minor objective responses. Overall, regorafenib showed fairly significant clinical value.

Optimally, a biomarker could be identified to help guide patient selection for regorafenib, as not all patients benefit. Moreover, it is also important to consider the best timing of regorafenib throughout the course of therapy. The CORRECT trial enrolled patients with a good per-

**Treatment in Third-Line Settings**

Two new agents are now available for patients with refractory metastatic CRC who have received 2 lines of therapy. Regorafenib is a multitargeted tyrosine kinase inhibitor. The combination drug trifluridine/tipiracil, also known as TAS-102, is a cytotoxic chemotherapeutic agent. Both regorafenib and trifluridine/tipiracil are approved by the US Food and Drug Administration (FDA) for use in patients with metastatic CRC who have already received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, for RAS-wild type tumors, anti-EGFR therapy.\textsuperscript{13,14}

Regorafenib and trifluridine/tipiracil differ in their mechanisms of action. Regorafenib is an oral multitargeted tyrosine kinase inhibitor that hits at least 19 different targets, each at pharmacologic doses. The targets include signaling components of growth pathways (ie, RAS) and angiogenesis (ie, VEGF). Trifluridine/tipiracil is an orally bioavailable cytotoxic agent. It is a fluorothymidine, but has a slightly different mechanism of action than 5-FU. Trifluridine is a thymidine-based nucleic acid analogue, and tipiracil is an inhibitor of thymidine phosphorylase. Tipiracil prevents trifluridine from degrading.\textsuperscript{15,16}

**Clinical Trial Data for Regorafenib**

The primary study that led to the FDA approval of regorafenib was the CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial, an international, multicenter, randomized, phase 3 trial that enrolled 760 patients with refractory metastatic CRC.\textsuperscript{17} Patients had refractory disease and a good performance status. Any RAS mutation status was allowed. Patients were assigned 2:1 to regorafenib at 160 mg/day or placebo once daily for the first 3 weeks of each 4-week cycle, plus best supportive care.

The primary endpoint, overall survival, was met. Regorafenib demonstrated a significant improvement in median overall survival over placebo (6.4 months vs 5.0 months, respectively; hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; 1-sided \( P = .0052 \); Figure 1). Regorafenib was also associated with an improvement in progression-free survival (PFS) over placebo, with a median PFS of 1.9 months vs 1.7 months, respectively (HR, 0.49; 95% CI, 0.42-0.58; \( P < .0001 \); Figure 2). Although the average survival benefit associated with regorafenib was relatively short at 1.4 months, some patients had a clear benefit for a prolonged period of time. As many as 20% of patients had stable disease for 6 months or longer. Although the Response Evaluation Criteria In Solid Tumors (RECIST) response rate was essentially 0, some patients did have minor objective responses. Overall, regorafenib showed fairly significant clinical value.

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---

**Figure 1.** Regorafenib improved median overall survival in the phase 3 CORRECT trial. CORRECT: Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. *Lancet*. 2013;381(9863):303-312.\textsuperscript{17}
formance status. It appears that a patient’s likelihood of benefitting from regorafenib is stronger earlier in the disease course before performance status begins to decrease.

The main adverse events associated with regorafenib include fatigue, hypertension, and hand-foot skin reaction, which can be problematic.\(^\text{17}\) Side effects such as fatigue and hand-foot skin reaction appear early, commonly within the first cycle of therapy. It is important to appropriately manage hand-foot syndrome in order to avoid excessive toxicity that lowers the likelihood of benefit.

The CONCUR Trial

The CONCUR (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial was a randomized, double-blind, placebo-controlled, phase 3 trial evaluating regorafenib in Asian patients with treatment-refractory metastatic CRC.\(^\text{18}\) Patients had received at least 2 prior lines of therapy or could not tolerate standard therapies, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of at least 3 months, and adequate organ function. A total of 204 patients were randomly assigned 2:1 to regorafenib plus best supportive care or placebo plus best supportive care. After a median follow-up of 7.4 months, regorafenib was associated with a significant improvement in survival over placebo (median overall survival, 8.8 months vs 6.3 months; HR, 0.55; 95% CI, 0.40-0.77; 1-sided \(P=\text{.00016}\); Figure 3).

The survival benefit with regorafenib in the CONCUR trial exceeded that observed in the CORRECT study.

Patients in the CONCUR trial were less heavily pretreated, as they were drawn from countries with more limited access to biologic agents. The demonstration of a greater survival benefit in this less heavily pretreated population suggests that earlier use of regorafenib may confer an even greater benefit. This finding is important to keep in mind in the United States, where the majority of patients are treated with almost all available biologic agents.

The CONSIGN Registry

Regorafenib was also evaluated in the CONSIGN (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy) registry, an open-label, phase 3b study designed to evaluate the toxicity and activity of regorafenib in a real-world clinical practice setting.\(^\text{19}\) As of January 2015, 2872 patients were included in the registry. Patients had an ECOG performance status of 0 to 1 and received regorafenib at 160 mg once daily for the first 3 weeks of each 4-week cycle.

The safety profile of regorafenib and the survival curves of enrolled patients were similar to those observed in the phase 3 trials.\(^\text{19}\) This large study validated in a clinical practice setting the benefit of regorafenib that was observed in the CORRECT and CONCUR trials. The estimated PFS was 2.8 months. Treatment-related adverse events of any grade occurred in 91% of patients. Adverse events higher than grade 3 occurred in 80%. Treatment-related AEs led 9% of patients to discontinue regorafenib, and 60% of patients required treatment modification.
Figure 3. Regorafenib improved median overall survival in the phase 3 CONCUR trial. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.18

![Graph showing overall survival comparison between Regorafenib and Placebo](image)

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<th>Placebo</th>
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HR, 0.77; 95% CI, 0.64-0.94; *P*=.0052


![Graph showing overall survival comparison between TAS-102 and Placebo](image)

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<th>Placebo</th>
</tr>
</thead>
<tbody>
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<td>459</td>
<td>294</td>
</tr>
<tr>
<td>294</td>
<td>137</td>
<td>64</td>
</tr>
<tr>
<td>64</td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.68 (95% CI, 0.58-0.81) *P*<.001
Clinical Trial Data for Trifluridine/Tipiracil

The efficacy and safety of trifluridine/tipiracil was evaluated in the double-blind, phase 3 RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 Plus Best Supportive Care [BSC] Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) trial, which randomly assigned 800 patients with refractory metastatic CRC in a 2:1 manner to receive trifluridine/tipiracil or placebo.20 The findings from this trial led to the approval of trifluridine/tipiracil in the United States. Trifluridine/tipiracil was significantly more effective than placebo as assessed by median overall survival (7.1 months vs 5.3 months; HR, 0.68; 95% CI, 0.58–0.81; P<.001; Figure 4) and median PFS (2.0 vs 1.7 months; HR, 0.48; 95% CI, 0.41–0.57; P<.001). The use of trifluridine/tipiracil was associated with a significant delay in worsening of ECOG performance status compared with placebo. The median time to an ECOG performance status of 2 or higher was 5.7 months with trifluridine/tipiracil vs 4.0 months with placebo (HR, 0.66; 95% CI, 0.56–0.78; P<.001). A benefit in overall survival was maintained among the patients who were pretreated with regorafenib in this trial (approximately 20% of the study population).

The most frequent adverse event associated with trifluridine/tipiracil is myelosuppression. In the RECOURSE trial, grade 3/4 neutropenia developed in 38% of patients treated with trifluridine/tipiracil.

Conclusion

Many ongoing clinical trials are evaluating the potential roles of regorafenib and trifluridine/tipiracil as components of combination regimens and in other treatment settings. Moreover, the treatment of metastatic CRC may continue to evolve as other novel agents are evaluated in the third-line setting. Many patients who require third-line therapy or beyond still have a good performance status. Therefore, there is clearly a need for new therapies.

Disclosure

Dr Marshall is on the speakers bureaus of, does research for, and consults for Amgen, Bayer, Taiho, and Genentech.

References

Optimal Use of Regorafenib: Dosing Strategies and Patient Selection

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The FDA-approved dosage of regorafenib, and the dosage used in the phase 3 clinical trials, is 160 mg (four 40-mg tablets) once daily for the first 21 days of each 28-day cycle. These dosage recommendations were established based on the phase 1, dose-escalation study that demonstrated tolerability. The main adverse events were hand-foot skin reaction, fatigue, voice changes, hypertension, and diarrhea. The adverse events associated with regorafenib tend to develop early in the course of therapy and attenuate over time, even if the dose is maintained. In the CORRECT study, the most common treatment-related adverse events of grade 3 or higher were hand-foot syndrome (17%) and fatigue (10%). The tolerability of regorafenib improved after the first 2 to 3 cycles of treatment in all of the randomized, phase 3 trials (CORRECT, CONCUR, and CONSIGN).

This pattern of improved tolerability over time is encouraging for patients who may benefit from long-term treatment with regorafenib. Stable disease, as confirmed by the first computed tomography scan after 8 weeks, occurs in approximately 40% to 45% of patients. A recent case report described an elderly woman with metastatic CRC who received regorafenib and achieved stable disease for 11 months. Dose modifications were used to manage adverse events.

Use in Clinical Practice

The finding that adverse events associated with regorafenib tend to develop early has consequences for clinical practice. It is critical that patients are monitored carefully in the first 1 to 2 cycles of treatment to detect and effectively manage early adverse events. In the CORRECT study, patients were seen every 2 weeks. In retrospect, this frequency was insufficient to capture early adverse events. Currently, in my own clinical practice, I speak with patients (either in person or on the telephone) after 1 week of treatment to discuss skin reactions and any other side effects. Patients visit the clinic to undergo liver enzyme testing every 2 weeks, at least for the first 2 cycles of treatment.

Dose Titration Strategies

The observation that the adverse effects associated with regorafenib tend to improve over time led to the concept of modifying the dosing strategy to improve tolerability. An incremental dose-escalation protocol is illustrated in Figure 5. An approach recognized as common practice by the National Comprehensive Cancer Network guidelines is to start at a lower dose (80 or 120 mg) and escalate based on tolerability, easing patients into treatment. Another strategy involves starting at a higher dose and titrating down. Both approaches are being evaluated in ongoing phase 2 studies that are assessing the safety benefit of different dosing strategies and determining whether alternative dosing adversely affects efficacy.

ReDOS (Regorafenib Dose Optimization Study) is an ongoing, randomized, phase 2 study comparing lower-dose vs standard-dose regorafenib in 120 patients with refractory metastatic CRC. Patients in the lower-dose arm start cycle 1 at 80 mg/day in week 1, 120 mg/day in week 2, and 160 mg/day in week 3. They then start cycle 2 at the previously tolerated dose. Patients in the standard-dose arm start at the 160-mg dose and then deescalate as needed for tolerability. The primary endpoint, which accounts for both efficacy and safety, is the proportion of patients in each arm who complete cycle 2, have no disease progression at the first computed tomography evaluation, and intend to start cycle 3.

The other phase 2 study is evaluating the safety and tolerability of a titrated dosing strategy in older patients with metastatic CRC. The trial plans to enroll 60 patients ages 70 years or older with metastatic CRC. Patients receive regorafenib at a starting dose of 120 mg/day in cycle 1, with the possibility of increasing the dose to 160 mg in subsequent cycles based on tolerability. The primary outcome is the number of patients who develop grade 3 to 5 toxicity. Other outcomes include response rates, association of adverse events with geriatric assessments, and quality of life.
Patient Selection for Regorafenib

For appropriately selected patients, regorafenib can have substantial benefit and induce durable responses. Patient selection is an important component of integrating regorafenib therapy into practice. Factors associated with a higher likelihood of response include a previous response to therapy, lower-volume disease, good performance status, and metastases confined to the lungs and not widespread (eg, to the lymph nodes). Not every patient with CRC should receive regorafenib. Regorafenib should be avoided in patients who are candidates for hospice rather than active therapy. Data indicate that patients with a poor performance status are unlikely to benefit from regorafenib, and they should therefore be spared treatment to avoid the potential toxicities.

A biomarker that can preselect patients for or against regorafenib has not yet been identified. Based on available data, the presence of \( \text{RAS} \), \( \text{RAF} \), or \( \text{BRAF} \) mutations does not affect responses to regorafenib. Therefore, the best marker is clinical judgment.

It should be noted that both regorafenib and trifluridine/tipiracil mainly induce stable disease, and not objective responses (tumor shrinkage).

Management of Adverse Events

When speaking with patients about initiating treatment with regorafenib, it can be helpful to explain that the goal is to complete the first 2 cycles, at which point the potential for benefit is typically known. Patient education, close monitoring, and preemptive management of adverse events are all essential before treatment begins. Education about potential adverse events should focus on hand-foot skin reaction (Figures 6 and 7). This event differs from the scaling and redness, known as hand-foot syndrome, observed with capecitabine. Hand-foot skin reaction has an inflammatory component that can result in blisters, particularly at pressure points on the feet. Patients should be informed of proper skin management techniques, such as removing callouses before starting therapy, softening the
skin with urea-based keratolytic creams and lotions, and wearing comfortable shoes to avoid aggravating pressure points on the feet. Regorafenib should be discontinued as soon as blistering or severe reddening at pressure points appear, as these adverse events can severely affect quality of life by impairing the ability to walk. Once these side effects resolve, regorafenib can be restarted either at the same dose or at a lower dose, depending on the severity of the symptoms. The decision is a matter of clinical judgment.

The preemptive approach is similar to the Skin Toxicity Evaluation Protocol With Panitumumab (STEP), which has been implemented as routine practice for patients starting an EGFR inhibitor. This strategy incorporates the preemptive use of skin moisturizers, sunscreen, topical corticosteroids, and doxycycline. The ReDOS study will assess the role of this approach for patients starting regorafenib.

Disclosure
The Mayo Clinic Foundation has received grants from Bayer and Taiho for research conducted by Dr Grothey.

References
Management of Metastatic Colorectal Cancer in the Community-Based Setting

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Management of metastatic CRC presents unique challenges for oncologists practicing in the community setting. One challenge lies in the number of clinicians available to treat the growing number of patients. Currently, there are approximately 13,000 practicing oncologists in the United States.1 In 2016, there will be approximately 134,500 diagnoses of large bowel cancer, including 95,000 colon cancers, in the United States.2 An estimated 49,700 patients died of colorectal cancer, representing 8% of cancer deaths.3 The overall cancer incidence is expected to increase by 45% from 2010 to 2030.3

The geographic distribution of practicing oncologists and other medical specialists is another issue. Many physicians are located in urban settings, with rural areas often lacking sufficient physician coverage in oncology and other specialties.1 According to data from the American Society of Clinical Oncology, only 6% of oncologists practice in rural areas, where 59 million Americans live.1 Community settings may also lack access to an interdisciplinary team, which is important in cancer care. Typically, academic centers have oncologists, nutritionists, palliative care specialists, social workers, and case managers all in the same facility. A community practice may not have these resources onsite. It can be challenging for the oncologist to assume all of these roles.

Characteristics of patients seeking treatment also differ based on the practice setting, and these differences may affect treatment strategies. Approximately 90% of patients in academic centers who enroll on clinical trials have a good ECOG performance status (0 or 1). In the community setting, however, the typical patient does not have such a high performance status, especially after failure of multiple lines of chemotherapy. These patients tend to have comorbidities, such as neuropathy, diabetes, hypertension, and pulmonary disorders. With the shortage of rural physicians, it can be difficult to ensure that these comorbidities are effectively treated. Oncologists may therefore need to manage these other conditions.

Currently, only 3% of adults with cancer participate in clinical trials.4 The majority of cancer patients are treated in community settings, whereas the majority of cancer patients who enroll in clinical trials are treated within academic centers. Additionally, trial populations are underrepresented by racial and ethnic minorities, the elderly, and low-income patients.5 Barriers to clinical trial participation for community physicians include financial burdens, regulatory complexity, lack of logistical support, decreased awareness of trial availability, and attitudes about participation.

Treatment Principles for Relapsed Metastatic Colorectal Cancer

Previously, patients with metastatic CRC who relapsed after standard therapy had few options other than supportive care. This approach has been shown to extend quality of life and survival in patients with metastatic non–small cell lung cancer.6 With the recent approvals of regorafenib and trifluridine/tipiracil, however, there are now options for third-line treatment in metastatic CRC.7,8 As discussed in the previous articles in this monograph, clinical trial data have confirmed the efficacy of these agents.9,10

Incorporating Newer Agents Into Practice

It is reasonable to offer regorafenib and trifluridine/tipiracil to all eligible patients. Trifluridine/tipiracil can be started at the full, recommended dose unless a patient has significant pancytopenia, in which case the dose should be reduced. If needed, a growth factor can be used.

When initiating regorafenib, the starting dose should be reduced to improve tolerability. Although the COR-
RECT trial used regorafenib at 160 mg; lower doses (eg, 120 mg) can reduce the likelihood of adverse effects, particularly hand-foot skin reaction.11 After starting therapy, clinicians should assess patients weekly in order to monitor for the development of side effects and administer treatment as needed. The dose of regorafenib is then adjusted based on tolerability. The ReDOS trial is evaluating different doses of regorafenib and will provide information about pharmacokinetic values and response rate.

Regorafenib should be taken at the same time each day with a low-fat meal that contains less than 600 calories and less than 30% fat. Patients should also be advised to store the pills in the original container instead of a pillbox, with the lid tightly closed.

### Monitoring for Adverse Events

At the beginning of treatment with regorafenib, patients should be monitored weekly for toxicities. The main side effects associated with regorafenib are fatigue and hand-foot skin reaction (Table 1), which are typically seen in the first cycle and decline thereafter.9 Patients may also develop the adverse events seen with other anti-VEGF inhibitors, such as hypertension, proteinuria, dysphonia, and impaired wound healing, as well as diarrhea and anorexia.

To minimize the risk of hand-foot skin reaction, patients should be instructed to use urea-based creams twice daily on their hands and feet. Patients with known hypertension should check their blood pressure daily; other patients can have their blood pressure checked at the weekly clinic visit. Patients should undergo weekly liver function tests and complete blood counts. Typically, by the end of cycle 2, if the patient is receiving a well-tolerated dose and their laboratory results have been stable, the frequency of clinic visits can be reduced.

The adverse events associated with trifluridine/tipiracil are primarily hematologic (Table 2); therefore, close monitoring is important for patients with known neutropenia, anemia, or thrombocytopenia. Patients may also develop fatigue. Laboratory assessments should be conducted weekly when starting therapy. After a well-tolerated dose is established, the frequency of clinic visits can be reduced.

### Selecting Among Newer Therapies

The selection of therapy is based on the patient’s performance status and tolerance to prior therapies. Trifluridine/tipiracil can be used either before or after regorafenib. In the RECURSE trial of trifluridine/tipiracil, approximately 20% of patients had received regorafenib.10 Patients can begin treatment with regorafenib and then switch to trifluridine/tipiracil after progression. It would also be appropriate to start with regorafenib in patients who developed pancytopenias from chemotherapy. Conversely, if a patient has existing severe hand-foot skin syndrome from prior therapy, then it may be more appropriate to start with trifluridine/tipiracil and switch to regorafenib after progression.

Patients receiving regorafenib or trifluridine/tipiracil should be evaluated for response after 8 weeks of treatment, at which point it will be possible to detect any benefit or stable disease. Patients who continue therapy should undergo evaluation every 8 weeks. Patients with stable disease may continue on treatment. Patients with slight disease progres-

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**Table 1.** Adverse Events (≤10%) Associated With Regorafenib in the CORRECT Trial

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<th>Any Grade (%)</th>
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<tr>
<td>Fatigue</td>
<td>47</td>
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<tr>
<td>Hand-foot skin reaction</td>
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CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. Lancet. 2013;381(9863):303-312.9

**Table 2.** Laboratory Abnormalities Associated With Trifluridine/Tipiracil (TAS-102) in the RECURSE Trial

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<th>Lab Parameter</th>
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<td>Leukopenia</td>
<td>77</td>
<td>21</td>
</tr>
<tr>
<td>Anemia</td>
<td>77</td>
<td>18</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Increase in total bilirubin</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>Increase in alkaline phosphatase level</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Increase in creatinine level</td>
<td>13</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Clinicians should remember that the treatment goal in these patients is palliation, not cure. The concept of continuing therapy that is providing benefit despite disease progression is becoming more common in the field of oncology.

In conclusion, survival for patients with metastatic CRC continues to improve with the introduction of new agents and the ability to continue therapy for longer durations. These steps reflect a movement toward managing metastatic CRC like a chronic disease.

Disclosure
Dr Seery is a speaker for Bayer and Ipsen. She is a member of the advisory boards of Halozyme, Bayer, and Genentech. Dr Tran has no real or apparent conflicts of interest to report.

References

Current Options for Third-Line Treatment of Metastatic Colorectal Cancer: Discussion
Axel Grothey, MD, John L. Marshall, MD, and Tara E. Seery, MD

H&O What are some approaches to sequencing therapy?

Axel Grothey, MD The overall philosophy in the continuum of care is to keep patients alive for as long as possible while maintaining the best quality of life for as long as possible in the palliative setting. We want to expose patients to all active agents to maximize the chances for a treatment response. Trifluridine/tipiracil and regorafenib have very different adverse event profiles. It is clear that patients with a deteriorated performance status should not receive regorafenib, and therefore the patient pool for trifluridine/tipiracil is larger. Trifluridine/tipiracil is a subjectively easier therapy to take. I would consider use of trifluridine/tipiracil in a patient with a performance status of 2.

When treating a patient with a good performance status, I would rather start with regorafenib before trifluridine/tipiracil. Use of trifluridine/tipiracil first could allow the patient’s performance status to deteriorate owing to tumor progression, which could prevent the patient from being a candidate for regorafenib. A patient with good performance status should be exposed to all active agents, which would be permitted by the use of regorafenib before trifluridine/tipiracil.

John L. Marshall, MD In the phase 3 RECURSE trial of trifluridine/tipiracil, previous use of regorafenib was reported in 27% of patients in Europe and 24.2% of patients in the United States. The goal is to administer these therapies while the performance status is still good.
**H&O** Do you have any further suggestions regarding how to manage adverse events associated with third-line agents?

**John L. Marshall, MD** With regorafenib, finding the right dose for each patient is key. With trifluridine/tipiracil, adverse events may one day be minimized with scheduling. With all new therapies, it takes a while to determine how best to manage the adverse events encountered in real-world settings. It is important to closely monitor patients for adverse events.

**Axel Grothey, MD** Proper education of patients is essential. Patients should be prepared for the potential adverse events, including fatigue or hand-foot skin reaction. Management strategies, including preemptive treatment for hand-foot skin reaction, should be implemented.

**Tara E. Seery, MD** If a patient receiving regorafenib develops grade 2 hand-foot skin reaction, the dose should immediately be reduced by 40 mg (1 pill). If the reaction recurs, the regorafenib should be held until the symptoms improve, at which time the therapy can be restarted. If patients develop symptomatic grade 2, grade 3, or grade 4 hypertension, then regorafenib should be stopped immediately and the hypertension should be treated. Regorafenib can be restarted at a lower dose. There is no single cure for the fatigue that can develop with regorafenib. Patients can be advised to exercise; some clinicians use low-dose corticosteroids or methylphenidate.

For patients receiving trifluridine/tipiracil, low blood counts should be managed with growth factors, transfusions, and iron supplementation. Dose reductions can be used if necessary. Fatigue is managed with the standard approaches.

**H&O** Are there any other common questions you receive?

**Tara E. Seery, MD** Patients ask about liver function alterations with regorafenib. I always check patients’ liver function tests, but I have not yet observed liver function elevations with regorafenib. Patients may ask about mutation status. Responses to both regorafenib and trifluridine/tipiracil have been observed in both KRAS-mutated and KRAS–wild-type patients. Mutation status is not a reason to withhold these therapies.

**References**

Slide Library

- **Metastatic Colorectal Cancer**
  - In the United States, there are nearly 133,000 new diagnoses of CRC each year.  
  - Approximately one-third of patients with CRC will develop metastatic disease.  
  - Most of these patients will develop relapsed/refractory disease.  
  - Most cases of metastatic CRC are incurable.

- **Treatment in Third-Line Settings**
  - **Regorafenib**
    - An oral multitargeted tyrosine kinase inhibitor that hits at least 19 different targets, each at pharmacologic doses.
  - **Trifluridine/tipiracil (TAS-102)**
    - An orally bioavailable cytotoxic agent.

- **Data for Regorafenib**
  - The Phase 3 CORRECT trial:
    - Evaluated regorafenib in Asian patients with treatment-refractory metastatic CRC who had received previous treatment with an investigational drug and one or more cytotoxic drugs.
    - Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-1 were enrolled.
    - The median progression-free survival was significantly longer in the regorafenib arm compared to placebo.

- **Data for Trifluridine/Tipiracil (TAS-102)**
  - The Phase 3 RECOUSE trial:
    - Evaluated the efficacy of trifluridine/tipiracil in patients with advanced refractory CRC who had received at least two prior regimens.
    - Patients with ECOG performance status 0-1 were enrolled.
    - The median overall survival was significantly longer in the trifluridine/tipiracil arm compared to placebo.

- **Clinical Use of Regorafenib**
  - Patient selection is an important component of integrating regorafenib therapy into practice. Patients with a poor performance status are unlikely to benefit from regorafenib.
  - Adverse events, such as hand-foot skin reaction and fatigue, tend to develop early and ameliorate over time. To minimize the risk of hand-foot skin reaction, patients should apply unabsorbable cream twice daily to their hands and feet.
  - Although the FDA-approved dosage is 160 mg four times daily, tolerability can be improved by starting at lower doses.
  - Regorafenib should be taken at the same time each day with a meal that contains less than 600 calories and less than 30% fat.

- **Clinical Use of Trifluridine/Tipiracil (TAS-102)**
  - Trifluridine/tipiracil can be started at the full, recommended dose except in patients with significant pancytopenia, who should receive a reduced dose.
  - The adverse events associated with trifluridine/tipiracil are primarily hematologic; therefore, close monitoring is important for patients with known neutropenia, anemia, or thrombocytopenia.
  - Patients may develop fatigue.

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