Abstract: In the setting of metastatic colorectal cancer, many gains in patient outcomes have been achieved throughout the last 2 decades. A primary driver of these gains is access to more lines of therapy. In the palliative metastatic setting, all patients ultimately progress and require continued treatment sequencing. The goal is to expose patients to all lines of available therapies. It is now possible to better select patients for each therapy. Treatment selection algorithms encompass disease factors and patient characteristics, such as overall condition and age. Appropriate molecular profiling assessments should be available early in the treatment course, to drive decision-making and allow use of alternative therapies when possible. The transition to third-line therapy can be prompted by changes in imaging scans or laboratory tests, as well as changes in the patient’s symptom burden. It can be problematic to delay initiation of third-line therapy when it is clinically indicated. Many oncologists will consider rechallenging patients with the same chemotherapy that did not work earlier. Although this strategy is reasonable, it should not necessarily take precedence over use of agents with proven efficacy in later lines of therapy in randomized clinical trials, such as regorafenib and trifluridine/tipiracil. Clinicians now commonly adjust the dose of regorafenib. A delay in the initiation of these third-line agents can allow the patient’s performance status to decrease, thus diminishing the opportunity for a successful outcome.
# Table of Contents

The Importance of Exposing Patients With Metastatic Colorectal Cancer to All Treatment Options  
Fotios Loupakis, MD, PhD  

Proactive Transitioning to Third-Line Treatment in Metastatic Colorectal Cancer  
Tanios S. Bekaii-Saab, MD  

Metastatic Colorectal Cancer: Strategies for Third-Line Treatment  
John L. Marshall, MD  

Q&A: Colorectal Cancer in Younger Patients  
John L. Marshall, MD, Tanios S. Bekaii-Saab, MD, and Fotios Loupakis, MD, PhD  

Slide Library  

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The Importance of Exposing Patients With Metastatic Colorectal Cancer to All Treatment Options

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Metastatic colorectal cancer (mCRC) is a heterogeneous disease. Throughout the past 2 decades, the survival of patients with mCRC has significantly improved, owing both to earlier diagnosis, as well as improvements in treatment options (Figure 1). Another factor that has markedly helped to improve patient outcomes is a better understanding of the fundamental disease biology, allowing better groupings of patients according to molecular and clinical features that define response to therapy.

Unlike other solid tumors, mCRC may be curable even in the setting of stage IV disease. Some patients with liver-only metastasis or isolated lung metastasis can undergo a radical resection. This subgroup has been the subject of several clinical trials. Advances have been made in the treatment of these patients in the neoadjuvant and adjuvant setting, with significant improvements in surgical resection techniques and strategies to define the ideal candidates for these approaches.

The disease is unresectable in more than 80% of patients diagnosed with stage IV mCRC. In this group of patients, new chemotherapeutic agents and active targeted molecules in the first-line setting represent important advances in management. Data have shown the importance of exposing patients to all available treatments throughout their treatment course, particularly upfront during the first and second lines of treatment.

Treatments for mCRC

In the past several years, varied schools of thought have arisen among clinicians regarding the treatment approach for patients with mCRC. On one side of the spectrum was a step-by-step strategy that incorporated gradual treatment intensification. First-line treatment consisted of low-intensity first-line therapy, generally with 1 or 2 drugs, and other agents were introduced when the disease progressed. On the opposite side of the spectrum was a...
strategy that began with an intensive multiple-drug regimen (eg, 5-fluorouracil, oxaliplatin, and irinotecan).

Evaluation of these different strategies showed that there is no single answer for all patients. As in many cases in medicine, it was necessary to identify which patients were best suited for which approach. Treatment selection algorithms therefore now encompass disease factors and patient characteristics, such as overall condition and age. Molecular status can now be used to tailor treatment on an individual basis. Specifically, the RAS mutation status can help guide selection of the best biologic agents to pair with chemotherapy. Because the RAS mutation defines resistance to anti–epidermal growth factor receptor (EGFR) therapy, agents targeting the vascular endothelial growth factor (VEGF) pathway are the only biologic approach available for these patients. Another treatment refinement involved modulating the intensity of chemotherapy.

Throughout the past several years, new groups of patients have been recognized. This has permitted a better definition of the molecular makeup of these tumors, beyond the RAS status. Other molecular aberrations have become important. The BRAF mutation is a prognostic factor that indicates poor outcomes. The presence of this mutation can change treatment, even in the first-line setting. BRAF-mutated disease is aggressive, and this knowledge can be used to select treatment. There are new agents approved in the second-line and later settings for patients with BRAF-mutated mCRC (eg, encorafenib).

It is also important to identify the subgroup of patients who have mismatch repair–deficient disease. This alteration has therapeutic implications. Recently, data from the phase 3 KEYNOTE-177 trial (A Phase III Study of Pembrolizumab [MK-3475] vs. Chemotherapy in Microsatellite Instability-High [MSI-H] or Mismatch Repair Deficient [dMMR] Stage IV Colorectal Carcinoma) suggested that use of pembrolizumab may change the prognosis and the natural history of this subgroup of patients. In this study, first-line pembrolizumab significantly improved median progression-free survival (PFS) vs chemotherapy (16.5 vs 8.2 months; hazard ratio [HR], 0.60; 95% CI, 0.45-0.80; \( P = 0.0002 \)). Although these patients are a small group (just 3% to 5% of mCRC cases overall), tailoring treatment can make all the difference for that single patient with this molecular alteration. For these patients, there is now the possibility for first-line treatment with an approach that could result in long-term disease control, and potentially even a cure.

**Table 1. Survival According to the Number of Treatments Received Among Patients With Metastatic Colorectal Cancer**

<table>
<thead>
<tr>
<th>The Number of Administered Available Drugs (n)*</th>
<th>MST, months (95% CI)</th>
<th>2-Year Survival Rate, % (95% CI)</th>
<th>3-Year Survival Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 (575)</td>
<td>15.3 (14.4-17.0)</td>
<td>35.9 (32.0-40.3)</td>
<td>24.9 (21.4-29.0)</td>
</tr>
<tr>
<td>4 (363)</td>
<td>24.4 (21.9-26.3)</td>
<td>50.3 (45.3-55.8)</td>
<td>27.8 (23.4-33.0)</td>
</tr>
<tr>
<td>5 (320)</td>
<td>28.4 (26.3-31.8)</td>
<td>60.0 (54.8-65.6)</td>
<td>33.1 (28.3-38.8)</td>
</tr>
<tr>
<td>6 (134)</td>
<td>36.0 (35.1-40.4)</td>
<td>81.1 (74.8-88.1)</td>
<td>51.4 (43.6-60.7)</td>
</tr>
<tr>
<td>7 (33)</td>
<td>37.3 (36.9-48.4)</td>
<td>87.9 (77.4-99.8)</td>
<td>65.9 (51.4-84.5)</td>
</tr>
</tbody>
</table>

*Rechallenge or investigational drugs were not included. Cetuximab and panitumumab were counted as one drug: an anti-EGFR antibody. Bevacizumab, ramucirumab, and ziv-aflibercept were counted as one drug: an anti-angiogenesis drug.

MST, median survival time.

Adapted from Kawakami T et al. ESMO abstract 2667. Ann Oncol. 2019;30(suppl 5).7

Data by Kawakami and colleagues confirmed the validity of an intuition that clinicians had 15 years ago: exposing patients with mCRC to all of the active treatments available can extend their survival expectancy (Table 1). This group retrospectively analyzed consecutive patients with mCRC who had received first-line chemotherapy between January 2005 and September 2016. Patients were divided into 3 groups according to the availability of active drugs at the initiation of first-line chemotherapy: cohort A (only cytotoxic drugs available), cohort B (molecular-targeting drugs available), and cohort C (regorafenib or trifluridine/tipiracil available as late-line treatment). The primary outcome of overall survival was numerically longest in cohort C. There was no significant difference between cohorts B and C. Further, conversion surgery had a great impact on improvement of overall survival, and this impact was comparable in cohorts A, B, and C. The median overall survival time of patients treated with 6 or more drugs exceeded 30 months. The median overall survival rose with the increasing number of agents used, from 15.3 months in patients treated with 3 or fewer drugs, 24.4 months in those treated with 4 or fewer drugs,
28.4 months in those treated with 5 or fewer drugs, 36.0 months in those treated with 6 or fewer drugs, and 37.3 months in patients treated with 7 or fewer drugs.

Disclosure

Dr Loupakis is a consultant for Astellas, Samsung Bioepis, Roche, Amal Therapeutics, Amgen, and Bayer.

References


Proactive Transitioning to Third-Line Treatment in Metastatic Colorectal Cancer

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In the palliative metastatic setting, all patients with colorectal cancer ultimately progress and require continued treatment sequencing. The goal is to expose as many patients as possible to all lines of available therapies.1 This goal is not always feasible, but it is important to keep in mind while sequencing agents.

Disease Course During Second-Line Therapy

Many gains in patient outcomes have been achieved throughout the last 2 decades.2 A primary driver of these gains is access to more lines of therapy. Importantly, however, it is also now possible to better select patients for each treatment. Approximately 80% to 90% of patients will be able to access second-line therapies. When moving from the second line to the third line, this percentage drops to between 50% and 70%. Some patients develop cumulative toxicities from the first 2 lines of therapies that impact performance status so much that further treatment is not possible. Patient preference should be discussed at every line of treatment. Ultimately, patient preference trumps any other factor when deciding on the next line of therapy.

When selecting third-line treatment, it is important to carefully consider what therapies were used in the first line and second line.3 Physicians must pay close attention to the intensification and deintensification strategies used. For example, a patient may have received intense therapy for 3 to 4 months and then moved to maintenance therapies (capecitabine, bevacizumab, or others), or a drug holiday may have been used.

For patients who progress through multiple lines of therapies, the duration of treatment becomes progressively shorter with every line of therapy. These shorter treatment durations are in part attributed to changes in the disease biology with time. As patients continue throughout the lines of therapy, they are selected for cancer cell clones that are more aggressive. These cells begin to dominate the cancer, and as a result, the patient’s overall status deteriorates. Patients tend to lose energy and muscle mass, and they may also develop some of the chronic toxicities associated with the treatment. A decreased performance status limits the extent of therapy that can be considered beyond the second-line setting. This observation stresses the importance of treatment selection in the first-line and second-line settings. The better we manage our patients in...
Switching to Third-Line Therapy

It is important for oncologists to consider later lines of therapy as part of the standard sequencing strategy, in order to establish a treatment continuum from first-line to second-line to third-line and beyond. Many oncologists will consider rechallenging patients with the same chemotherapy that did not work earlier. Although this strategy is reasonable, it should not necessarily take precedence over use of agents with proven efficacy in later lines of therapy in randomized clinical trials, such as regorafenib and trifluridine/tipiracil (Figures 2 and 3).

The transition to third-line therapy can be prompted by changes in imaging scans or laboratory tests, as well as by changes in the patient's symptom burden. Several factors fit into the larger picture of progressive disease. It is not just an imaging scan or a biomarker, but also clinical symptoms. Often, these signs and symptoms do not progress together. For example, the carcinoembryonic antigen (CEA) levels can rise, but the scans look stable and the patient feels well. In this case, it would probably not be the right time to move from second-line to third-line therapy. In contrast, if the patient is becoming more symptomatic and the scans look even slightly worse, it might be time to consider initiation of third-line therapy, even if the CEA level is nearly unaffected.

It can be problematic to delay initiation of third-line therapy when it is clinically indicated. At this point, patients start to lose their ability to benefit from treatment with third-line agents, or they may even lose their ability to begin these therapies. Therefore, there are benefits to consider a prompt switch when it makes clinical sense to move to the third-line setting and beyond.
A remarkable aspect of the treatment of mCRC is that a patient’s prognosis is not predictable upon first presentation. For example, it is not known whether the patient will have a rocky course with aggressive disease, and use up all lines of therapy quickly, or whether he or she will live for many years with metastatic disease. Currently, even with the many available treatment tools, it is difficult to predict a patient’s outcome.

It is important to strive for a longer marathon strategy of treatment when managing patients with mCRC. There is increasing evidence that survival is improved with more intense first-line therapy with combinations such as leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) or those targeting EGFR. Whether this improvement is related to an increased depth of response, or some other factor, is not known. A more aggressive frontline approach will employ more of the available treatments, highlighting the importance of using newer agents in later lines.

Most patients now reach third-line treatment and beyond. I am old enough to remember when physicians were eager for any medicine that could improve survival for patients with mCRC. We seem to have lost some of this eagerness recently. Some clinicians appear to believe that these newer therapies have less value than some others that confer a similar survival benefit. Clinicians should be aware of the data supporting these newer agents, and prioritize their use in order to maximize the survival of patients.

Options in the Third-Line Setting

Currently, 2 agents—regorafenib and trifluridine/tipiracil—are approved by the US Food and Drug Administration specifically in the third-line setting for mCRC. Both agents are indicated for use in patients previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biologic

References

therapy, and an anti-EGFR therapy (if RAS wild-type).3,4 In addition, other targeted agents have gained approval for certain subsets of patients with specific molecular profiles. For example, the checkpoint immunotherapy agents nivolumab and pembrolizumab are indicated for the treatment of patients with tumors that are microsatellite instability–high or mismatch repair–deficient.5,6 The indication of nivolumab is restricted to patients with mCRC that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, whereas pembrolizumab is approved in the first-line mCRC setting. Additionally, patients with tumors that have NTRK fusions are candidates for treatment with the NTRK inhibitors larotrectinib and entrectinib, both of which carry tumor-agnostic indications.7,8

Clinical Data Supporting the Use of Regorafenib in mCRC

Clinical Trial Data Supporting Regorafenib

The approval of regorafenib in mCRC was in part based on data from the CORRECT trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy).9 CORRECT was a randomized, double-blind, placebo-controlled phase 3 clinical trial that evaluated regorafenib in patients with mCRC whose disease had progressed following treatment with all standard therapies approved at the time. Because this was an international study—conducted across North America, Europe, Asia, and Australia—the definition of standard therapy varied but must have included (as licensed locally) a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and either cetuximab or panitumumab (in patients with RAS wild-type disease). All patients in the study received best supportive care, and were randomly assigned to treatment with regorafenib (160 mg daily for the first 3 weeks of a 4-week cycle; n=505) or placebo (n=255).

The primary endpoint of the CORRECT study, overall survival, was met.9 The median overall survival was 6.4 months in the regorafenib arm vs 5.0 months in the placebo arm (HR, 0.77; 95% CI, 0.64-0.94; P=.0052). A secondary endpoint, PFS, was also significantly prolonged with regorafenib vs placebo. The median PFS was 1.9 vs 1.7 months, respectively (HR, 0.49; 95% CI, 0.42-0.58; P<.0001). Notably, there was no significant difference in the objective response rate between the 2 arms (1.0% vs 0.4%, respectively), and no complete responses were observed in either treatment arm. The disease control rate, which included patients who achieved a partial response or stable disease, was 41% with regorafenib vs 15% with placebo (P<.0001).

Dose modifications owing to adverse events were reported in 67% of the regorafenib arm vs 23% of the placebo arm.9 A total of 61% of patients in the regorafenib arm required a dose interruption, while 38% required a dose reduction. Adverse events were most common during the first or second treatment cycle. Fatigue (47% with regorafenib vs 28% with placebo) and hand-foot skin reaction (47% vs 8%, respectively) were the most common adverse event of any grade. Grade 3 or 4 treatment-related adverse events were reported at a higher incidence in the regorafenib arm compared with the placebo arm. The most common regorafenib-related grade 3 or higher adverse events were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation.

Following the positive results of the CORRECT study, the CONCUR study (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was conducted to confirm the efficacy and safety of regorafenib in a broader population of Asian patients.10 Although the Asian population enrolled in the CORRECT trial was primarily composed of Japanese patients, the CONCUR study enrolled patients across China, Hong Kong, South Korea, Taiwan, and Vietnam. Other design and enrollment criteria were generally the same between the 2 clinical trials. The study randomly assigned 136 patients to treatment with regorafenib and 68 patients to placebo. All patients received best supportive care.

The CONCUR study confirmed the results of the CORRECT study, showing that regorafenib significantly prolonged the primary endpoint of overall survival. The median overall survival was 8.8 months with regorafenib vs 6.3 months with placebo (HR, 0.55; 95% CI, 0.40-0.77; 1-sided P=.00016; Figure 4).10 As was previously demonstrated in the CORRECT study, the secondary endpoint of PFS also improved with regorafenib. The median PFS was 3.2 months with regorafenib vs 1.7 months with placebo (HR, 0.31; 95% CI, 0.22-0.44; 1-sided P<.0001). The objective response rate was low, limited to partial responses, and similar between the 2 arms (4% with regorafenib and 0% with placebo; 1-sided P=.045). When patients with stable disease were considered in the disease control rate, there was a significant benefit with regorafenib vs placebo (51% vs 7%, respectively; 1-sided P<.0001).

Regorafenib showed a similar safety profile in CONCUR, with treatment modifications (dose interruption, dose reduction, or both) owing to adverse events more frequent with regorafenib (71%) vs placebo (16%).10 Treatment discontinuation owing to an adverse event occurred in 14% of the regorafenib arm and 6% of the placebo arm. Treatment-related grade 3 or higher adverse events occurred in 54% of the regorafenib arm vs 15% of the placebo arm.
Real-World Data Supporting Regorafenib

Following the CORRECT and CONCUR trials, several studies were published demonstrating the use of regorafenib in real-world populations of patients. The CONSIGN study (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy) characterized the safety profile of regorafenib in a large patient population that was considered more representative of patients with treatment-refractory mCRC.11 CONSIGN was a prospective, open-label, single-arm phase 3b study conducted throughout Europe, North America, Israel, and Australia. The enrollment criteria were similar to the CORRECT study. A total of 2864 patients received regorafenib, administered at the standard dose of 160 mg once daily for the first 3 weeks of a 4-week cycle. Median PFS, the only efficacy endpoint measured, was 2.7 months (95% CI, 2.6-2.7). The rate of PFS was 15% at 6 months and 4% at 12 months. An exploratory analysis suggested that patients with longer PFS (4 months or longer) were more likely to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, no liver metastases, and a longer time since the diagnosis of metastatic disease vs patients with a PFS of less than 4 months. The safety profile of regorafenib in the CONSIGN study aligned with the previously reported trials, and included a 46% rate of dose reductions and a 9% rate of treatment discontinuations owing to treatment-emergent adverse events.

CORRELATE was a prospective, observational clinical study that evaluated regorafenib dosing and related tolerability among a real-world, international population of 1037 patients with mCRC.12,13 Among these patients, 57% initiated regorafenib at the approved dose of 160 mg. The remaining patients initiated treatment at the lower doses of 120 mg (30%) or 80 mg or lower (13%).

The primary objective was safety.12,13 A total of 80% of regorafenib-treated patients developed a treatment-emergent adverse event of any grade that was considered related to regorafenib. The most common of these events were fatigue (41%), hand-foot skin reaction (26%), diarrhea (19%), mucositis (15%), hypertension (14%), and anorexia (13%). A total of 36% of regorafenib-treated patients experienced a grade 3 or higher treatment-emergent adverse event that was considered related to regorafenib. The most common of these events were fatigue (9%), hand-foot skin reaction (7%), and hypertension (6%). Secondary objectives of CORRELATE focused on determining the clinical activity of regorafenib in this real-world population. The median overall survival was 7.6 months (95% CI, 7.1-8.2), and the median PFS was 2.9 months (95% CI, 2.8-3.0; Figure 5).

A large, prospective, postmarketing surveillance study was conducted in Japan to examine the safety and efficacy of regorafenib for the treatment of mCRC in a Japanese population.14 A total of 1227 patients were included. Regorafenib was administered at the recommended dose of 160 mg once daily for the first 3 weeks of a 4-week cycle. This dose of regorafenib was initiated in 65.4% of patients; the remaining patients initiated treatment at a daily dose of 120 mg (21.6%) or lower (13.0%).

A total of 33% of patients discontinued treatment after experiencing an adverse drug reaction for which a causal relationship with regorafenib could not be excluded.14 Approximately one-half of patients (51.8%)

Figure 4. Median overall survival in the phase 3 CONCUR trial, which compared regorafenib vs placebo. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy; HR, hazard ratio. Adapted from Li J et al. Lancet Oncol. 2015;16(6):619-629.10
experienced a potentially related adverse drug reaction of grade 3 or higher. These events included hand-foot skin reaction (19.2%), hypertension (15.6%), liver injury (11.5%), thrombocytopenia (4.7%), and decreased appetite (2.7%). In a landmark analysis, several factors were associated with a significant effect on overall survival. Those associated with improved overall survival included resection of the primary site, the presence of hand-foot skin reaction on day 28, and the rectum as the primary site of disease. Factors associated with reduced overall survival included ascites, metastasis in the liver, metastasis in the bone, an ECOG performance status of 2 or higher, and a body surface area of less than 1.6 m².

The Czech CORECT registry is a noninterventional postmarketing database for patients with CRC treated with targeted agents across several oncology centers in the Czech Republic. The most recent analysis included 555 patients with disease progression during or after prior systemic therapy, who were treated with regorafenib. Among 472 patients who had completed treatment with regorafenib and were evaluable for response, a partial response was reported in 13 patients (2.8%), and disease stabilization occurred in 130 patients (27.5%). The median PFS was 3.5 months (95% CI, 3.2-3.7), and the median overall survival was 9.3 months (95% CI, 8.3-10.3). In a multivariable analysis, female sex, longer interval from diagnosis of metastatic disease, M0 stage at diagnosis, and an ECOG performance status of 0 were associated with longer overall survival. The authors noted that the overall survival reported among this set of patients treated with regorafenib in the real-world clinical practice exceeded that reported in randomized trials of regorafenib.

Clinical Data Supporting the Use of Trifluridine/Tipiracil in mCRC

The approval of trifluridine/tipiracil was primarily based on data from the double-blind, randomized, phase 3 RE COURSE trial (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). A total of 800 patients with refractory mCRC were randomly assigned to treatment with up to 4 cycles of 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. All patients in both arms also received best supportive care.

The primary endpoint of overall survival was improved in patients treated with trifluridine/tipiracil. The median overall survival was 7.1 months with trifluridine/tipiracil vs 5.3 months with placebo (HR, 0.68; 95% CI, 0.58-0.81; P < .001). The median PFS, a secondary endpoint, was 2.0 months with trifluridine/tipiracil vs 1.7 months with placebo (HR, 0.48; 95% CI, 0.41-0.57; P < .001). The objective response rate was 1.6% with trifluridine/tipiracil vs 0.4% with placebo, but this difference did not reach statistical significance (P = .29). When stable diseases was included in this analysis, the disease control rate was
significantly higher with trifluridine/tipiracil vs placebo (44% vs 16%, respectively; \( P < .001 \)).

Grade 3 or higher adverse events were more common with trifluridine/tipiracil vs placebo.16 These adverse events included hematologic toxicities (neutropenia [38% vs 0%], anemia [18% vs 3%], and thrombocytopenia [5% vs <1%]), as well as nonhematologic toxicities (nausea [2% vs 1%], vomiting [2% vs <1%], and diarrhea [3% vs <1%]).

Results from the RECOURSE trial were subsequently confirmed in the randomized, double-blind, placebo-controlled phase 3 TERRA trial (Study of Trifluridine/Tipiracil [Also Known as S95005 or TAS-102] in Patients With a Pretreated Colorectal Cancer That Has Spread (Metastatic); PS, performance status. Adapted from Bachet JB et al. ESMO Open. 2020;5(3):e000698.18)

Real-World Data Supporting Trifluridine/Tipiracil
The phase 3b PRECONNECT study (An Open-Label Early Access Phase IIb Study of Trifluridine/Tipiracil [S95005/TAS-102] in Patients With a Pretreated Metastatic Colorectal Cancer) provided a real-world look at the safety and efficacy of trifluridine/tipiracil.18 Among 793 patients from 13 countries, 79.8% had withdrawn from the study owing to progressive disease at the time of data cutoff (after receiving trifluridine/tipiracil for a median of 2.84 months). Among 414 patients who received trifluridine/tipiracil and underwent a postbaseline tumor evaluation, the median PFS was 2.8 months (95% CI, 2.7-2.0), and the disease control rate was 34.4% (95% CI, 31.1%-37.9%). Across subgroups, the median PFS was numerically higher in patients with a baseline ECOG performance status of 0 vs 1 (3.2 vs 2.3 months) and in those who had previously received 2 lines or fewer of treatment compared with more than 2 lines (3.1 vs 2.7 months).

A total of 73.9% of patients reported at least one grade 3 or higher adverse event, and 33.5% experienced a serious adverse event (considered related to trifluridine/tipiracil in 8.8% of patients).18 The most frequent grade 3 or higher treatment-related adverse events were neutropenia (38.2%) and anemia (6.5%). The median time to deterioration in the patients’ ECOG performance status was 8.9 months (Figure 6). One patient died at home as a result of diarrhea and vomiting, which was considered related to trifluridine/tipiracil.

Adverse events required a reduction in the dose of trifluridine/tipiracil in 8.8% of patients.18 These events were considered treatment-related in 7.7% of patients, and included neutropenia (3.4%), diarrhea (1.0%), and anemia (0.9%). Adverse events led to interruption or delay of trifluridine/tipiracil in 46.3% of patients. These events were drug-related in 37.8%, and the most common was neutropenia (30.9%).

Optimizing Treatment With Regorafenib
When regorafenib was first introduced, the eagerness for a new agent led to use in some patients who were not
good candidates. For example, the treatment may have been used in patients who lacked a good performance status or who had liver function abnormalities. Clinicians have since learned important lessons regarding the use of regorafenib concerning both dosing and patient selection. The initial clinical trials of regorafenib and trifluridine/tipiracil were conducted in patients with an excellent performance status (ECOG performance status of 0 or 1). Selecting this type of patient for treatment, rather than patients with a fairly rapidly declining status, will improve success rates.

A high rate of toxicities was apparent in both of the clinical trials that established the use of regorafenib in the third-line setting of mCRC. This observation was confirmed in follow-up real-world studies. Often, these toxicities required either dose reductions or treatment interruptions, which can interfere with the maximal clinical activity a patient may reach with regorafenib. More recently, strategic approaches to dosing have been used to mitigate these toxicities, primarily pioneered in the ReDOS trial (Regorafenib Dose Optimization Study). For patients randomly assigned to the dose-escalated schedule, regorafenib was initiated at 80 mg (administered as 2 tablets daily) during the first week, then increased to 120 mg daily during week 2, and finally up to the standard dose of 160 mg daily during week 3. Patients were assessed from week to week to determine whether the dose could be increased over time, based on the toxicities experienced by each individual patient. For the dose-escalated schedule, the dose of regorafenib in the second cycle was determined by the maximal dose that was tolerated during the first cycle. In both arms, treatment was continued for 3 weeks on and 1 week off.

To measure the potential benefit of this altered regorafenib dosing schedule, the primary endpoint in the ReDOS trial was the proportion of patients who completed 2 cycles of therapy and initiated the third cycle. This endpoint was met by 43% of patients in the dose-escalated arm vs 26% in the standard-dose arm (1-sided \( P = 0.043 \)). The median overall survival was 9.8 months in the dose-escalated arm vs 6.0 months in the standard-dose arm, but this difference did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank \( P = 0.12 \)). Dose modifications occurred in 9 patients (22%) in the dose-escalated group and 15 patients (32%) in the standard-dose group. No dosing delays were required in the dose-escalation group, whereas a delay occurred in 7 patients (15%) in the standard-dose group.

In general, the incidence of grade 3 adverse events commonly associated with regorafenib—such as fatigue, hand-foot skin reaction, hypertension, and diarrhea—was...
lower in the dose-escalated group compared with the standard-dose group during both cycle 1 and cycle 2 of treatment. In a prespecified analysis of cycle 1, the incidence of grade 2 or 3 hand-foot skin reaction was lower in the dose-escalated group vs the standard-dose group. The most frequent grade 3 or 4 adverse events included fatigue (13% with the escalated dose vs 18% with the standard dose), hand-foot skin reaction (15% vs 16%), abdominal pain (17% vs 6%), and hypertension (7% vs 15%). Serious adverse events were reported in 26% of patients in the dose-escalated arm and 34% of patients in the standard-dose arm. Abdominal pain was the most frequent serious adverse event in both groups (13% and 6%, respectively).

The cumulative dose of regorafenib was similar in both treatment groups, suggesting that the overall regorafenib exposure during the first 2 cycles was more important than the dose of regorafenib. The ReDOS investigators concluded that the alternative dose-escalation strategy evaluated in this study was an effective approach that allowed optimization of regorafenib dosing with comparable activity and lower incidence of adverse events. Two ongoing phase 2 trials, RECC (Regorafenib Dose Escalation Therapy for Patients With Refractory Metastatic Colorectal Cancer) and RE-ARRANGE (Study Comparing Different Dose Approaches of Induction Treatment of Regorafenib in mCRC), are designed to compare different dose-escalation and scheduling strategies for regorafenib in mCRC, which may in turn provide further insight into the optimization of the dosing of this agent.

In the clinic, implementation of the ReDOS strategy requires that clinicians be better managers of patients. The clinician should not send the patient off with a prescription and a plan to follow-up in a month. Instead, it is necessary to build infrastructure to follow these patients through their first treatment cycle (at least), in order to optimize the dose. I inform patients that regorafenib results in stable disease in approximately half of cases, and that approximately a quarter of patients will have stable disease for up to 6 months.

Sequencing in the Third-Line Setting and Beyond

In the current era, there are several treatment options for patients who develop progressive disease after oxaliplatin- or irinotecan-based regimens in the first- and second-line, usually with a biologic in combination. Clinicians who are active in clinical trials begin to think about suitable studies. Another option is to start an approved third-line therapy, such as regorafenib or trifluridine/tipiracil. It is important to recognize that a delay in the initiation of these third-line agents can allow the patient’s performance status to decrease, thus diminishing the opportunity for a successful outcome. It is essential to maintain anticancer therapy for most of these patients, even while considering the third-line and fourth-line therapeutic options.

In the setting of third-line treatment and beyond, options include regorafenib and trifluridine/tipiracil. In some patients, rechallenge is possible, either with an anti-EGFR therapy or even with an oxaliplatin- or irinotecan-based chemotherapy regimen that was stopped to shift to a maintenance approach. As I am deciding among these options, I first consider whether the patient is in need of a response. Among patients who are symptomatic or who have a performance status suggesting that a lack of a response will lead to a rapid decline, regorafenib or trifluridine/tipiracil may not be good choices. These agents may not be tolerable for these patients, and they are unlikely to induce a much-needed response. In these cases, I would use an anti-EGFR agent or rechallenge with chemotherapy (if that is an option).

Alternatively, patients with a good performance status whose tumor burden is not immediately critical in terms of symptoms are good candidates for regorafenib or trifluridine/tipiracil. I tend to rely on regorafenib first, primarily because it provides a fundamental change in the mechanism of action being used to treat the cancer (Table 2). Although trifluridine/tipiracil is effective in fluoropyrimidine-refractory patients, it does not provide that fundamental mechanistic change.

Also factored into this decision is the side effect profile of each agent, and what toxicities the patient has

### Table 2. Regorafenib: Mechanisms of Action

<table>
<thead>
<tr>
<th>Angiogenesis</th>
<th>Inhibition of Tumor Metastasis</th>
<th>Oncogenesis</th>
<th>Tumor Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Regorafenib inhibits the VEGF receptors 1, 2, and 3</td>
<td>• Inhibition of tumor metastasis is thought to occur through both antiangiogenic and antiproliferative mechanisms</td>
<td>• Regorafenib blocks multiple oncogenic pathways, including RAF-1, RET, and KIT</td>
<td>• Regorafenib inhibits CSF1R, a tyrosine kinase receptor that is involved in macrophage proliferation</td>
</tr>
<tr>
<td>• Regorafenib inhibits the FGF receptors 1 and 2, the angiopoietin 1 receptor TIE2, and the PDGF receptors alpha and beta</td>
<td></td>
<td>• Regorafenib may work in concert with anti–PD-1/PD-L1 antibodies to augment the anticancer immune response</td>
<td></td>
</tr>
</tbody>
</table>
experienced before this point. For example, what is the condition of their bone marrow or their skin? What is their social situation? How strong was their adherence to the treatment regimen? Most patients who are candidates for either regorafenib or trifluridine/tipiracil will ultimately also be a candidate for the other agent. In most cases, it is possible to use both agents.

It is critical that clinicians incorporate these newer therapies with known survival advantages in as many patients with mCRC as possible. As we have gained experience in their use, we now see that chemotherapy can be given after either regorafenib or trifluridine/tipiracil and some early data suggest it might be possible to improve or restore activity of previously given agents by altering the sequence. The open-label, randomized, phase 2 REVERCE trial (A Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Previously Treated Wild-Type KRAS Metastatic Colorectal Cancer Patients) compared the sequence of regorafenib followed by cetuximab (n=51) vs the reverse sequence of cetuximab followed by regorafenib (n=50). Cetuximab was administered with or without irinotecan. The study, which was conducted in Japan, was stopped early after slow enrollment and a lack of funding. All patients had locally advanced CRC or mCRC that was KRAS wild-type. Their ECOG performance status was 0 to 2. Patients were stratified according to the study site, history of treatment with bevacizumab, and intention to use irinotecan with cetuximab. The patients continued to receive treatment until disease progression, unacceptable toxicity, or withdrawal. The primary endpoint of overall survival was 17.4 months in patients treated with regorafenib followed by cetuximab vs 11.6 months in those treated with cetuximab followed by regorafenib (HR, 0.61; 95% CI, 0.39-0.96; P=.0293; Figure 8).

Clinicians should aim to find the places throughout the treatment course where these agents fit, and then implement treatment in the smartest way possible. Do not leave survival on the table. Appropriate molecular profiling assessments should be available early in the treatment course, to drive decision-making and allow use of alternative therapies when possible. It is also necessary for clinicians to educate their patients about the entire treatment course early in the disease, so that the patients can be active participants in decision-making.

**Disclosure**

Dr Marshall has received funds from Genentech, Bayer, Amgen, Taiho, Ipsen, Celgene, and Caris.
References


Q&A: Colorectal Cancer in Younger Patients

John L. Marshall, MD, Tanios S. Bekaii-Saab, MD, and Fotios Loupakis, MD, PhD

John L. Marshall, MD What are your thoughts on the observation that we are seeing more and more patients with onset of CRC at a younger age?

Tanios S. Bekaii-Saab, MD We are certainly seeing more and more patients with CRC who present with a younger onset. For the most part, these patients present with left-sided tumors, often closer to the sigmoid and rectum. Progression to metastatic disease is frequent, and in my experience, these younger patients tend to possess a somewhat more aggressive disease (although the site of occurrence is slightly more favorable). For these younger patients with mCRC, my goal for treatment is to be as aggressive as possible. I consider initiating treatment with a triplet therapy combination, with folic acid, 5-fluorouracil, oxaplatin, and irinotecan (FOLFOXIRI) plus bevacizumab as the standard regimen. I have been using this triplet regimen more often.

John L. Marshall, MD I have, as well. I do not think we know why this disease is arising in younger patients. It could be environmental. It is clearly not just inherited cancer syndrome that is contributing to the rise in these younger patients. One interesting hypothesis is related to changes in the microbiome.

There has been a shift in screening recommendations to include younger people. An important and related element is that our allied physicians, including emergency room physicians, primary care physicians, and even obstetricians/gynecologists, should recognize that CRC can occur in younger patients, so that they do not simply wave off gastrointestinal bleeding or altered bowel habits in this group.

Tanios S. Bekaii-Saab, MD Yes, and they should not just assume that symptoms indicate irritable bowel syndrome or hemorrhoids. CRC is a real problem in these younger...
patients. We see patients as young as in their 20s, and even younger than that, which is a tragedy. Although the recommended age for first colorectal screening was recently decreased to 45 years—and I suspect the recommended age will drop by 5 years every few years or so—this problem will likely still continue to encompass a large group. In the United States, we tend to see these younger onset CRC cases in African Americans, as well as in some low socioeconomic groups in Appalachia. When I was at Ohio State approximately 10 years ago, the first trends in a younger population were noted in the Appalachian region (Kentucky, southern Indiana, and southern Ohio), where patients were presenting with CRC in their 20s and 30s.

John L. Marshall, MD My cases were coming from law firms and Capitol Hill. This increase in younger patients was not simply explained by bad health habits or obesity. Significantly, it is a global trend that we are also seeing in Europe and Asia.

John L. Marshall, MD I am cynical about the latest recommendation to start colonoscopy screening at age 45 years. I do not think that these tumors start with a polyp or otherwise provide a long lead time. Instead, I predict that while these earlier colonoscopies may begin to help identify cancer in some patients, a bigger impact would be seen with a more effective stool test or a circulating tumor cell blood test.

Fotios Loupakis, MD, PhD I agree. For at least 50% of these early-onset CRC cases, we do not know anything about the background. There are many suggestions. Changes in the microbiome is one of the more fashionable explanations currently, but evidence is lacking.

I do think colonoscopy screening will help, but will likely result in diagnoses of more cancers at a late stage. Of course, it is reasonable to try this strategy, as well as to start thinking about other ways to detect these cases even earlier.

John L. Marshall, MD We should also think about this in terms of our discussion regarding lines of therapy for metastatic disease. These cases are in younger patients—they are not retired, they are working full time, and they often carry the health insurance for the family. They have to keep working, keep raising their children, and keep living, which further complicates management of their mCRC. Therefore, these younger patients have social issues and dilemmas that traditionally have not weighed heavily in our treatment decisions. With increased recognition of these factors, however, clinicians are now learning how to best support these younger patients.

Tanios S. Bekaii-Saab, MD I agree. These active younger patients in particular might benefit from de-intensification strategies. Drug holidays are fine after intense chemotherapy, and they do not significantly change patient outcomes. We no longer treat to neuropathy or collapse; we want to treat just enough. Regardless of what line of treatment, 3 to 4 months of intense chemotherapy is likely more than enough, followed by maintenance therapy or a chemo-break.

Another important consideration is that, just like all other patients with mCRC, these younger patients may benefit from biologic modifiers, and even immunotherapeutics, if indicated. We need to ensure that every patient’s tumor gets sequenced from day 1, particularly in the United States, where there are these capabilities. A true understanding of the underlying molecular signature of the tumor has the potential to open up more doors for treatment beyond chemotherapy for many of these patients. Unfortunately, in my experience, I do not find many targets to go after. What about your experience?

John L. Marshall, MD I agree. There are not that many patients who stand out with a targetable molecular signature, which creates testing fatigue for many doctors. They do their due diligence, but often do not gain much information to impact treatment.

One way I am trying to be a better doctor myself—and also encouraging our fellows to do so—is to follow a strategy borrowed from the breast cancer community. In that setting, the first line of the patient history lists the patient’s age and sex, as well as results of molecular testing. In the breast cancer world, this is defined as estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, or human epidermal growth factor receptor 2 (HER2)-positive. In the CRC world, it needs to be microsatellite instability status, and RAS or BRAF status. In this way, it immediately shows what testing has been done (or not done), and allows us to keep better track of this information. This kind of change will help in terms of the science as well as we move forward, because it teaches us to think in these categories.

Tanios S. Bekaii-Saab, MD I like that idea. When I see patients coming from referrals, a chief complaint is the need to dig so deeply into the patient’s history to try to find any type of molecular testing or next-generation sequencing.

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Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array BioPharma, Genentech, Novartis, Mirati, Merus, AbGenomics, Incyte, Pfizer, and BMS. He has received consulting fees (directed to his institution) from Ipsen, Array BioPharma, Pfizer, Seattle Genetics, Bayer, Genentech, Incyte, and Merck. He has received consulting fees (directed to himself) from Boehringer Ingelheim, Janssen, Eisai, Daiichi Sankyo, Natera, Treos Bio, Celularity, Exact Science, Sobi, BetGene, Xilis, AstraZeneca, and Foundation Medicine. He is a member of independent data monitoring committees/data and safety monitoring boards (with fees directed to himself) for AstraZeneca, Exelixis, Lilly, PanCAN, and 1Globe. He is a member of the Scientific Advisory Boards of Imugene, Immuneering, and Sun BioPharma. He reports the following inventions/patents: WO/2018/183488 and WO/2019/055687. Dr Loupakis is a consultant for Astellas, Samsung Bioepis, Roche, Amal Therapeutics, Amgen, and Bayer.

References

**Metastatic Colorectal Cancer: Treatment Goals**

- In the palliative metastatic setting, all patients with colorectal cancer ultimately progress and require continued treatment sequencing.
- The goal is to expose as many patients as possible to all lines of available therapies.
- This goal is not always feasible, but it is important to keep in mind while sequencing agents.

**Treatment Selection in Metastatic Colorectal Cancer**

- Treatment selection algorithms encompass disease factors and patient characteristics, such as overall condition and age.
- Molecular status can be used to tailor treatment on an individual basis.
  - *RAS* mutation status can help guide selection of the best biologic agents to pair with chemotherapy.
  - The *BRAF* mutation is a prognostic factor that indicates poor outcomes. The presence of this mutation can change treatment, even in the first-line setting.
- It is also important to identify the subgroup of patients with mismatch repair deficient disease.

**Use of All Available Agents**

- Kawakami and colleagues retrospectively analyzed consecutive patients with mCRC who had received first-line chemotherapy between January 2005 and September 2016.
- The median overall survival rose with the increasing number of agents used:
  - ≤3 drugs: 15.3 months
  - ≤4 drugs: 24.4 months
  - ≤5 drugs: 28.4 months
  - ≤6 drugs: 365 months
  - ≤7 drugs: 37.3 months

*MCRC, metastatic colorectal cancer.*

**Initiation of Third-Line Therapy**

- It can be problematic to delay initiation of third-line therapy when it is clinically indicated.
- At this point, patients start to lose their ability to benefit from treatment with third-line agents, or they may even lose their ability to initiate treatment with these therapies.
- There are benefits to considering a prompt switch when it makes clinical sense to move to the third-line setting and beyond.

**Progressive Disease**

- For patients who progress through multiple lines of therapies, the duration of treatment becomes progressively shorter with every line of therapy.
- These shorter treatment durations are in part attributed to changes in the disease biology with time. As patients continue throughout the lines of therapy, they are selected for cancer cell clones that are more aggressive. These cells begin to dominate the cancer, and as a result, the patient’s overall status deteriorates.
- A decreased performance status limits the extent of therapy that can be considered beyond the second-line setting. This observation stresses the importance of treatment selection in the first-line and second-line settings.

**Transitioning to Third-Line Therapy**

- The transition to third-line therapy can be prompted by changes in imaging scans or laboratory tests, as well as changes in the patient’s symptom burden.
- Identification of progressive disease should encompass results from imaging scans and biomarkers, as well as clinical symptoms.
- Often, signs and symptoms do not progress in tandem.
**Third-Line Treatments**

- In the setting of third-line treatment and beyond, options include regorafenib and trifluridine/tipiracil.
- In some patients, rechallenge is possible, either with an anti-EGFR therapy or with an oxaliplatin- or irinotecan-based chemotherapy regimen that was stopped to shift to a maintenance approach.
- Patients with a good performance status whose tumor burden is not immediately critical in terms of symptoms are good candidates for regorafenib or trifluridine/tipiracil.

EGFR, epidermal growth factor receptor.

**Managing the Treatment Course**

- Clinicians should aim to find the places throughout the treatment course where these agents fit, and then implement treatment in the smartest way possible.
- Appropriate molecular profiling assessments should be available early in the treatment course, to drive decision-making and allow use of alternative therapies when possible.
- Clinicians should educate their patients about the entire treatment course early in the disease, so that the patients can be active participants in decision-making.

**The ReDOS Trial of Regorafenib**

- The randomized phase 2 ReDOS trial evaluated whether regorafenib-associated toxicities could be minimized with an escalated dosing schedule.
- The primary endpoint in the ReDOS trial was the proportion of patients who completed 2 cycles of therapy and initiated the third cycle. This endpoint was met by 43% of patients in the escalated-dosing arm vs 26% in the standard-dosing arm (1-sided P=0.043).
- Nearly twice as many patients in the escalated-dosing arm were able to achieve at least stable disease after 2 cycles of regorafenib, an improvement attributed to the longer duration of treatment.


**Chemotherapy**

- It is critical that clinicians incorporate the newer therapies with known survival advantages in as many patients as possible.
- Chemotherapy can be given after either regorafenib or trifluridine/tipiracil.
- Early data suggest that it might be possible to improve or restore activity of previously given agents by altering the sequence.

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