Clinical Roundtable Monograph

How to Incorporate a Chemo-Free Interval Into the Management of Metastatic Colorectal Cancer

Moderator

Axel Grothey, MD
Director, GI Cancer Research
West Cancer Center and Research Institute
OneOncology
Germantown, Tennessee

Discussants

Fortunato Ciardiello, MD, PhD
Department of Precision Medicine
University of Campania Luigi Vanvitelli
Naples, Italy

John L. Marshall, MD
Chief, Division of Hematology/Oncology
Medstar Georgetown University Hospital
Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Director, Otto J. Ruesch Center for the Cure of Gastrointestinal Cancers
Georgetown Lombardi Comprehensive Cancer Center
Georgetown University
Washington, DC

Abstract: Management of metastatic colorectal cancer reflects a continuum of care. The primary treatment goals are to prolong survival while maintaining the best quality of life. The recommended standard-of-care treatments in the first-line setting consist of combination chemotherapy regimens, given with or without biologic agents. Most patients will receive different lines of therapy for the rest of their life. In the context of lifelong therapy, incorporating chemo-free intervals is one strategy to help achieve these treatment goals. A principle of management is to ensure that all potentially active agents are available to patients. Third-line options for patients with an inadequate response to first-line and second-line therapy include regorafenib and trifluridine/tipiracil. These treatments should be initiated before the patient's performance status deteriorates. Patient characteristics should guide selection. The management plan now incorporates new lessons learned during the current global COVID-19 pandemic. One of the primary guiding principles underlying these recommendations is to avoid unnecessary clinic and hospital exposure. Telemedicine permits the remote management of patients who are receiving oral therapies. Many of these strategies will likely remain in place after the pandemic ends.

Clinical Advances in
HEMATOLOGY&ONCOLOGY ™
A Peer-Reviewed Journal

Table of Contents

Why Chemo-Free Treatment Intervals Can Improve Care of Patients With Metastatic Colorectal Cancer

Fortunato Ciardiello, MD, PhD

Department of Precision Medicine
University of Campania Luigi Vanvitelli
Naples, Italy

It is important to recognize the goals of treatment when managing patients with metastatic colorectal cancer (mCRC). Most patients will receive different lines of therapy for the rest of their lives. (A cure may be possible in a subgroup of patients with metastases limited to the liver.) For all patients, the primary treatment goals are to prolong survival while maintaining the best quality of life. In the context of lifelong therapy, incorporating chemo-free treatment intervals is one strategy to help achieve these goals.

The recommended standard-of-care treatments in the first-line setting consist of combination chemotherapy regimens, given with or without biologic agents.[1] For most of these treatments, use is recommended until the patient develops disease progression or unacceptable toxicity. In the real-world setting, however, patients generally reach a maximal response after 3 to 6 months of treatment. After that, the chemotherapy agent may be withdrawn. The biologic agent is potentially continued as a maintenance treatment, although the benefit of maintenance therapy following first-line treatment is unclear. For example, many patients undergo first-line treatment with oxaliplatin plus a biologic agent.[2] After reaching a maximal response, typically within 6 months, the oxaliplatin is removed and the biologic agent is continued as maintenance treatment. In many patients, treatment after first-line therapy is stopped not because of side effects or disease progression, but rather to provide a break from chemotherapy.

After 4 to 6 months of intensive chemotherapy, most patients undergo a depotentiation of chemotherapy, or even fully stop treatment, before any signs of disease progression arise. As a result, when patients inevitably begin treatment with a second-line regimen, most are not resistant to their first-line treatment. (An exception would be those patients who progress very early.) Therefore, in these patients, it is possible to reintroduce the first-line option with the hope that the tumor will once again respond to that treatment.[3] In cases when the first-line treatment was providing maximum activity and efficacy, the second-line regimen usually consists of a chemotherapy doublet, when tolerable.

Another important issue is the patient's duration of exposure to chemotherapy as a component of the typical regimens used in the first-line and second-line settings. Clinicians should consider a chemo-free third line of treatment, particularly in patients with a very long interval before progression after first-line treatment and a relatively long interval after second-line treatment. These patients present the best opportunity for use of treatments that are chemo-free and offer other mechanisms of action. In this context, the best opportunity is the use of a multikinase inhibitor, such as regorafenib, which blocks several different pathways that are directly or indirectly related to activation of the microenvironment and angiogenesis (Table 1).[4] Another widely used regimen in the third-line setting is trifluridine/tipiracil.[5] Although not supported by phase 3 data, rechallenge with first-line therapy is also an option in the third-line setting. This option is reserved primarily for patients who are *RAS* wild-type. Epidermal

Table 1. Regorafenib: Mechanisms of Action

Angiogenesis
• Regorafenib inhibits the VEGF receptors 1, 2, and 3
• Regorafenib inhibits the FGF receptors 1 and 2, the angiopoietin 1 receptor TIE2, and the PDGF receptors alpha and beta
Inhibition of Tumor Metastasis
• Inhibition of tumor metastasis is thought to occur through both antiangiogenic and antiproliferative mechanisms
Oncogenesis
• Regorafenib blocks multiple oncogenic pathways, including RAF-1, RET, and KIT
Tumor Immunity
• Regorafenib inhibits CSF1R, a tyrosine kinase receptor that is involved in macrophage proliferation
• Regorafenib may work in concert with anti–PD-1/PD-L1 antibodies to augment the anticancer immune response

FGF, fibroblast growth factor; PD-1, programmed cell death 1; PDGF, platelet-derived growth factor; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.
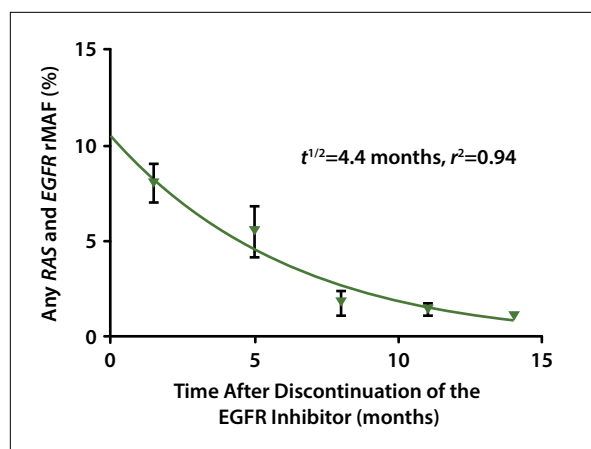
Figure 1. Exponential decay of the *RAS* and *EGFR* alleles in a study of patients with *RAS/BRAF* wild-type metastatic colorectal cancer treated with an anti-EGFR therapy who acquired *RAS* and/or *EGFR* mutations during therapy. EGFR, epidermal growth factor receptor; rMAF, relative mutant allele frequency. Adapted from Parseghian CM et al. *Ann Oncol.* 2019;30(2):243-249.[9]

growth factor receptor (EGFR) inhibitors, if used as first-line treatment, may also be an option.

Rationale for a Chemo-Free Interval

There are several reasons to consider a chemo-free interval in the third-line setting. Data show that the overall response rate decreases as the patient moves through lines of therapy.[6-8] Stable disease increases in the second-line setting. A longer duration between frontline therapy with an anti-EGFR agent and rechallenge with an anti-EGFR agent corresponds to a better response to the latter treatment. This duration allows time for the clones to decay (Figure 1).[9] Data also support the benefits of a time interval between frontline oxaliplatin and rechallenge with oxaliplatin.[10,11]

Regorafenib is a viable treatment during the chemo-free interval. As discussed below, use of regorafenib extends overall survival and may help extend the interval until rechallenge with an anti-EGFR agent.[12]

Third-Line Options

In clinical practice, the best third-line options for patients with an inadequate response to first-line and second-line treatments are trifluridine/tipiracil and regorafenib.[4,5] In appropriate candidates, regorafenib is my preference, particularly to avoid the toxicities that are associated with chemotherapy, such as myelosuppression.[4] In Italy, the first-line course of chemotherapy is typically intensive and aggressive. Even patients who reach third-line treatment in relatively good health have bone marrow toxicity that would preclude a further round of chemotherapy. Trifluridine/tipiracil was associated with myelosuppression in

clinical trials, and may induce neutropenia, anemia, and thrombocytopenia in these patients.[3] Instead, an agent like regorafenib may be more appropriate.

Throughout the course of management, it is important to monitor the patient's well-being as he or she receives multiple lines of treatment for metastatic disease. There are now different treatment options with unique mechanisms of action and, as a result, different toxicity profiles. In my opinion, the best use of the anti-angiogenic agent regorafenib would be in the third-line setting, as opposed to later lines of therapy. It is clear that regorafenib works better in disease that is primarily cytostatic and not aggressively growing. Intervals with chemo-free therapy may help ensure that patients receive the right treatments at the right time.

Strategic approaches to dosing have mitigated the toxicities initially associated with regorafenib. Per data from the ReDOS trial (Regorafenib Dose Optimization Study), clinicians now adjust the dose of regorafenib to the patient.[13] When regorafenib stabilizes disease in the third-line setting, there is the opportunity for patients to receive long-term treatment with a noncytotoxic therapy. The optimal duration of therapy may be more achievable with a personalized dosing strategy. The ReDOS study is described in greater detail in a later article.

After Third-Line Therapy

A patient who develops disease progression after third-line therapy could be rechallenged with chemotherapy or an anti-EGFR agent, such as cetuximab or panitumumab. The REVERCE trial (A Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Previously Treated Metastatic Colorectal Cancer Patients) provides an example of the benefit associated with using regorafenib prior to an anti-EGFR agent.[12] REVERCE was an open-label, randomized, phase 2 trial that compared the sequence of regorafenib followed by cetuximab (n=51) vs the reverse sequence of cetuximab followed by regorafenib (n=50). In either case, cetuximab could be administered with or without irinotecan. The primary endpoint was overall survival. The study was conducted in Japan and enrolled 101 patients. It was stopped prematurely owing to slow enrollment and a lack of funding.

All patients had locally advanced CRC or mCRC that was *KRAS* wild-type, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients were stratified by study site, history of treatment with bevacizumab, and intention to use irinotecan with cetuximab. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal.

Overall survival was 17.4 months with the sequence of regorafenib followed by cetuximab vs 11.6 months
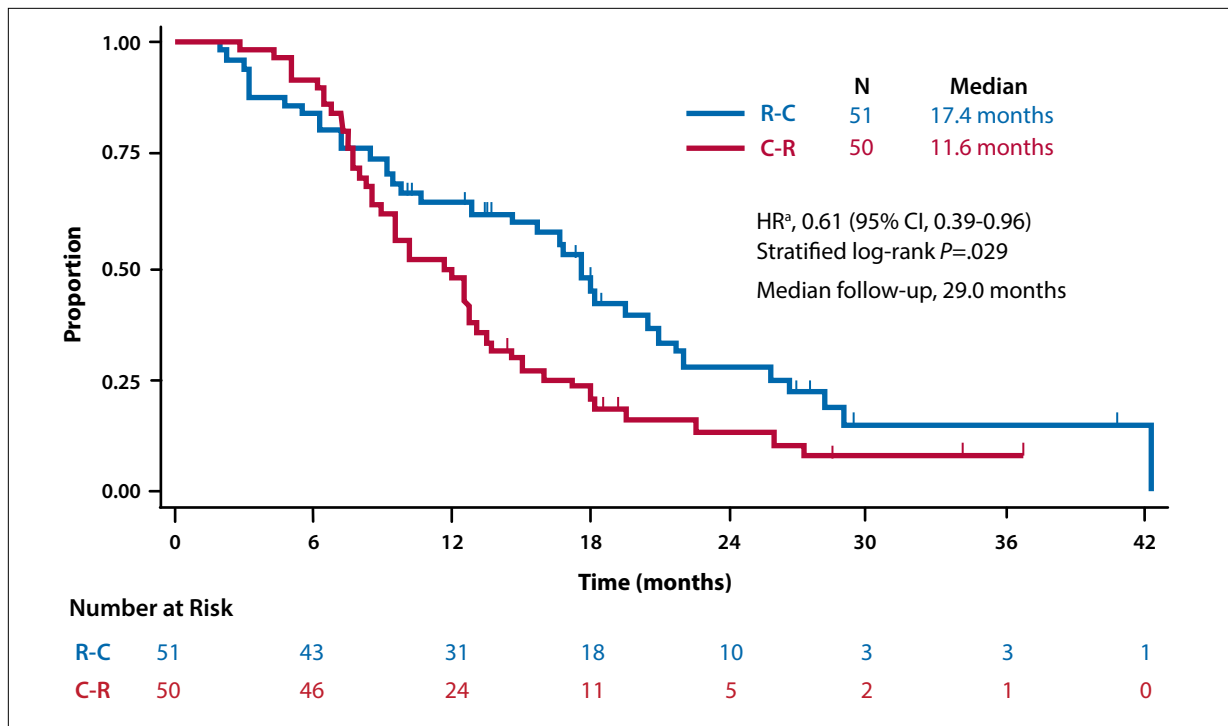
Figure 2. Overall survival in the phase 2 REVERCE trial, which compared the sequence of regorafenib followed by cetuximab (R-C) vs the sequence of cetuximab followed by regorafenib (C-R). [a]Adjusted by intention to use irinotecan. HR, hazard ratio; REVERCE, Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan. Adapted from Shitara K et al. *Ann Oncol.* 2019;30(2):259-265.[12]

with the sequence of cetuximab followed by regorafenib (hazard ratio [HR], 0.61; 95% CI, 0.39-0.96; *P*=.0293; Figure 2).[12] Following the first treatment in the sequence, *RAS* mutations were detected in the circulating tumor DNA (ctDNA) more often in patients treated with cetuximab first (n=11) vs regorafenib first (n=1). Other emerging gene mutations were identified at a greater frequency following cetuximab vs regorafenib. Patients with these gene mutations had worse overall survival outcomes compared with wild-type patients.

Disclosure

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Third-Line Treatments for the Management of Metastatic Colorectal Cancer: Why to Change the Mechanism of Action After Frontline Chemotherapy, and Insights Into Management During the COVID-19 Pandemic

John L. Marshall, MD

Chief, Division of Hematology/Oncology
Medstar Georgetown University Hospital
Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Director, Otto J. Ruesch Center for the Cure of Gastrointestinal Cancers
Georgetown Lombardi Comprehensive Cancer Center
Georgetown University
Washington, DC

Treatment of mCRC is complicated, primarily owing to the large amount of research that has been generated throughout the past several years. Colon cancers were initially managed as one disease, which was treated through sequential lines of therapy. This treatment paradigm has become more complicated in 2 main ways. First, colon cancer is now classified into different molecular subtypes. Rare subtypes are categorized according to microsatellite instability and *BRAF* mutation status. Additionally, there are less-understood subtypes of right-sided vs left-sided colon cancer and younger vs older age. A second complicating factor is the complexity in how patients respond to different treatments. Additionally, in some patients, metastases can be resected or treated locally.

Deciding to Initiate Third-Line Treatment

What was formerly a fairly linear pathway of treatment decisions has become a more complicated chess game, in which there is no exact answer for every patient. Instead, there are several strategies, and clinicians must understand how each of them work. It is then a matter of applying each of these strategies to the appropriate patient. The definition of earlier and later lines of therapy has become vague, and it can be unclear how to best apply them in which patients. As in a chess game, clinicians must pay attention to their hunches. In many cases, treatment decisions must be made in the absence of firm molecular evidence.

Among patients with mCRC, disease progression is defined by imaging scans that show increased tumor lesions, elevated levels of biomarkers, or the development of new symptoms from the cancer. These imaging scans, biomarkers, and clinical symptoms are the primary factors used to make decisions about changing lines of therapy. It must also be recognized that there are different severities of progression. Patients with small tumor burdens that have doubled in size differ from those with very large tumor burdens that have doubled in size. It is necessary to consider different treatment strategies for these types of patients.

A fundamental mistake that oncologists make today is to withhold medicines with known survival advantage until later lines of therapy. Agents such as regorafenib and trifluridine/tipiracil are essentially ineffective in patients with a rapidly declining performance status. However, the preference in the United States is to rechallenge with chemotherapy, instead of moving to one of these oral agents with a known survival advantage. It is necessary to implement these strategies earlier in the process, before the patient's performance status deteriorates. Therefore, clinicians must monitor patients closely, in order to implement treatment with these agents at optimal time points.

Options for Third-Line Treatment

The many options for later lines of therapy include oral agents such as regorafenib or trifluridine/tipiracil, anti-EGFR agents such as cetuximab, and rechallenge with the same cytotoxic chemotherapy used in earlier lines

of therapy. Selection among these options is based on the individual patient's disease characteristics, personal priorities and preferences, and history of treatment-related adverse events (AEs).

I prioritize regorafenib and trifluridine/tipiracil in patients with good performance status and reasonable tumor burden, for whom stable disease is a good result. In contrast, if a tumor response is needed and the patient has not yet received cetuximab or another anti-EGFR targeted approach, these agents would have a higher priority.

Regorafenib

In mCRC, regorafenib is indicated for the treatment of patients who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, a vascular endothelial growth factor (VEGF) inhibitor, and, if RAS wild-type, an anti-EGFR therapy.[1] Regorafenib is a multitargeted therapy, with a unique mechanism of action that inhibits multiple aspects of tumor biology and tumor-host interaction. A small molecule that inhibits multiple membrane-bound and intracellular kinases involved in normal cellular functions and pathologic processes, regorafenib acts in a 4-pronged manner, targeting tumor angiogenesis, metastasis, oncogenesis, and immunity. Colon cancer is a complex molecular disease, with multiple abnormalities and many dysregulated signaling pathways. It is likely that this multimodal mechanism of action is one of the reasons regorafenib works well in patients with this complex disease.

Regorafenib does not induce tumor regression, but clinical trials show it can stabilize disease.[2,3] Importantly, this disease stabilization translates to significantly prolonged progression-free survival and overall survival. Therefore, the patients best suited to receive regorafenib are those with a good performance status, and for whom stable disease is an acceptable option. Responses are infrequent after second-line regimens, and even more rare after third-line therapy. These are the patients in whom achieving and maintaining stable disease is an appropriate next step. Thus, in patients with a good performance status and reasonable tumor burden, regorafenib is an ideal drug. The efficacy and safety of regorafenib in this setting were established in 2 clinical trials: CORRECT (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) and CONCUR (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy).[2,3]

The CORRECT trial 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.[2] Because this was an international study (conducted across North America, Europe, Asia, and Australia), these standard therapies varied but had to include as many of the following as were licensed locally: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and either cetuximab or panitumumab (in patients with KRAS wild-type mCRC). All patients had an ECOG performance status of 0 or 1.

Patients were randomly assigned to treatment with regorafenib at 160 mg/day (n=505) or matching placebo (n=255).[2] In both arms, patients received treatment once daily for the first 3 weeks of each 4-week cycle. Best supportive care was administered to patients in both arms. Treatment was continued until disease progression, death, unacceptable toxicity, withdrawal of consent, or physician decision. At randomization, the patients were stratified according to prior treatment with VEGF-targeted drugs (yes or no), time from diagnosis of metastatic disease (≥18 months or <18 months), and geographic region (North America, western Europe, Israel, and Australia vs Asia vs eastern Europe).

Most baseline characteristics were similar between the regorafenib and placebo arms, with the exception of the proportion of patients with a KRAS mutation (54% vs 62%, respectively). The median age in both arms was 61 years. At baseline, 49% of patients in the regorafenib arm and 47% of patients in the placebo arm had received 4 or more prior systemic therapies.[2]

The study met the primary endpoint of overall survival.[2] The median overall survival was 6.4 months with regorafenib vs 5.0 months with placebo (HR, 0.77; 95% CI, 0.64-0.94; P=.0052; Figure 3). This overall survival benefit was observed across most patient subgroups. One exception was those patients with primary disease in the colon and rectum; however, this subgroup analysis was limited by a small patient number.

The median progression-free survival, a secondary endpoint, was longer with regorafenib compared with placebo (1.9 months vs 1.7 months; HR, 0.49; 95% CI, 0.42-0.58; P<.0001).[2] The Kaplan-Meier curves showed a clear separation after the median progression-free survival. The overall response rate was low (1.0% with regorafenib and 0.4% with placebo), and no complete responses occurred. The disease control rate, which included patients who achieved stable disease, was 41% with regorafenib vs 15% with placebo (P<.0001).

In the regorafenib arm, 67% of patients required a dose modification owing to an AE, compared with 23% in the placebo arm.[2] The modifications in the regorafenib arm consisted of a dose reduction in 38% and a dose interruption in 61%.

Fatigue and hand-foot skin reaction were the most frequently reported AE of any grade in patients treated with regorafenib, each occurring in 47% of this arm.[2] Most
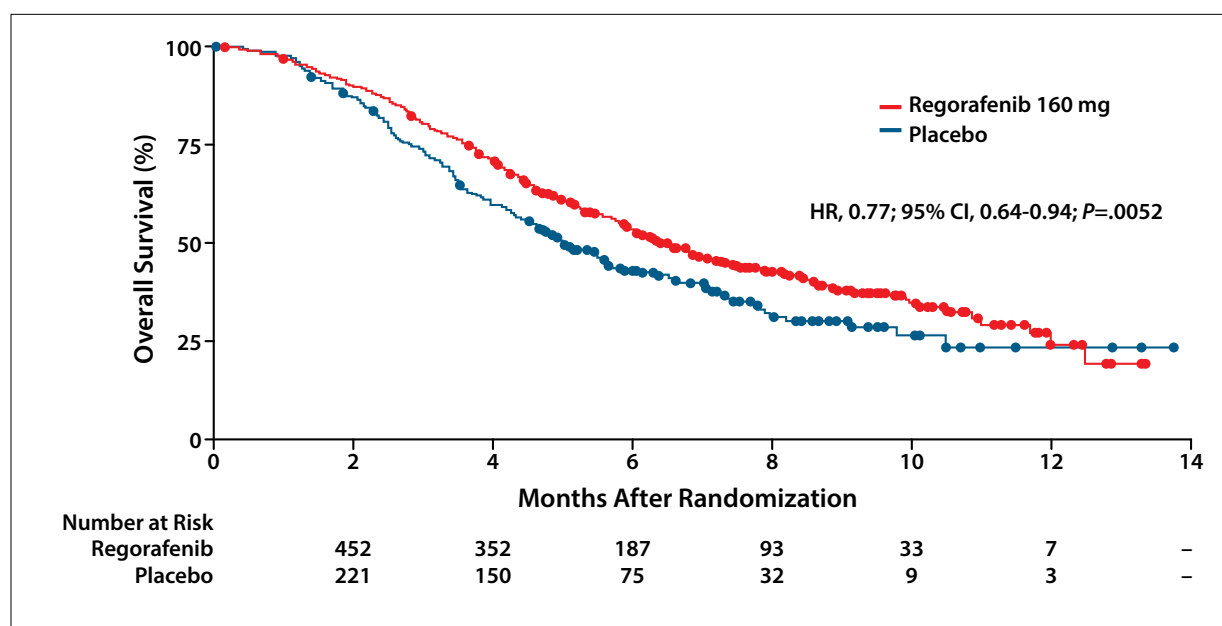
Figure 3. The median overall survival with regorafenib vs placebo in the phase 3 CORRECT trial. CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. *Lancet.* 2013;381(9863):303-312.[2]

AEs occurred during the first or second treatment cycle. Grade 3 or 4 treatment-related AEs occurred in 54% of the regorafenib arm vs 14% of the placebo arm. The most common regorafenib-related grade 3 or higher AEs were hand-foot skin reaction (17%), fatigue (10%), diarrhea (8%), hypertension (7%), and rash or desquamation (6%).

The CONCUR study was a randomized, double-blind, placebo-controlled, parallel-group phase 3 trial.[3] This design was similar to that of the CORRECT study,[2] but aimed to confirm the efficacy and safety of regorafenib in a broad population of patients with refractory mCRC located throughout China, Hong Kong, South Korea, Taiwan, and Vietnam. A key difference between the 2 studies was that CONCUR allowed enrollment of patients who had not been treated with a biologic agent, in consideration that these drugs were not widely available in some Asian countries at the time of the trial. Among the overall study population, 40% had not previously received any targeted biologic agent.

Patients were randomly assigned to treatment with either regorafenib at 160 mg (n=136) or matching placebo (n=68), administered daily for the first 3 weeks of each 4-week cycle.[3] At randomization, patients were stratified according to the number of metastatic sites (single vs multiple organs) and time from diagnosis of metastatic disease (<18 months vs ≥18 months). Patients in both arms also received best supportive care. Treatment was administered until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the treating physician.

Compared with the CORRECT trial, patients enrolled in the CONCUR trial were slightly younger (median age, 56.5 years).[2,3] At baseline, 63% of the study population had received 3 or more lines of treatment for mCRC. A total of 54% of patients in the regorafenib arm and 51% of patients in the placebo arm had received 4 or more prior systemic therapies.

The primary endpoint of the CONCUR trial, overall survival, was met.[3] 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). An exploratory analysis was conducted to evaluate the effect of previous targeted biologic treatment. The analysis suggested that the survival benefit associated with regorafenib was stronger in less heavily pretreated patients, in particular with regard to prior biologic agents.

The median progression-free survival, a secondary endpoint, was 3.2 months with regorafenib compared with 1.7 months with placebo (HR, 0.31; 95% CI, 0.22-0.44; 1-sided *P*<.0001).[3] The overall response rate was low, at 4% with regorafenib and 0% with placebo (1-sided *P*=.045). No responses were complete. The disease control rate, including patients with stable disease, was 51% with regorafenib vs 7% with placebo (1-sided *P*<.0001).

Treatment-related grade 3 or higher AEs occurred in 54% of the regorafenib arm and 15% of the placebo arm.[3] The most common grade 3 or higher AE reported in the regorafenib arm was hand-foot skin reaction, followed by hypertension, hyperbilirubinemia, hypophosphatemia, increase in alanine aminotransferase concentration,
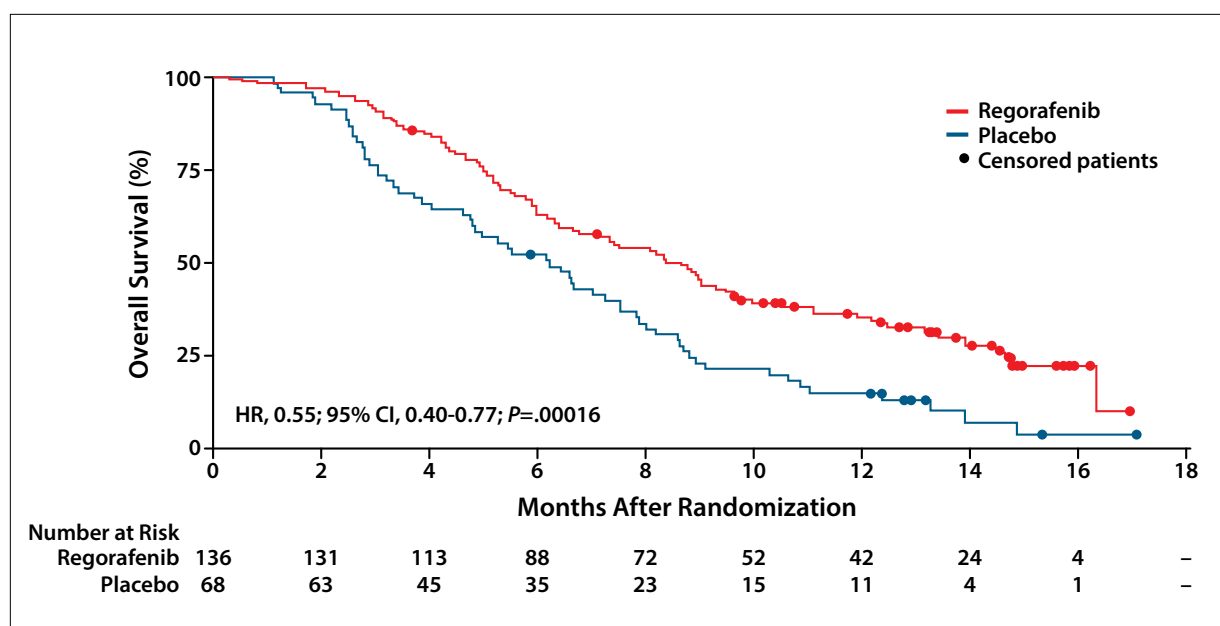
Figure 4. The median overall survival with regorafenib vs placebo in the phase 3 CONCUR trial. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy; HR, hazard ratio. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.[3]

increase in aspartate aminotransferase concentration, increase in lipase concentration, and maculopapular rash. AEs resulted in treatment discontinuation in 14% of the regorafenib group and 6% of the placebo group; most of these AEs were laboratory abnormalities. AEs resulted in treatment modification (treatment interruption, dose reduction, or both) in 71% of regorafenib-treated patients and 16% of placebo-treated patients.

I prefer to use regorafenib relatively early in the course of therapy, as it provides the patient with a chemo-free interval while still treating the tumor with a targeted therapy. As these clinical trials showed, there is good evidence showing that treatment with regorafenib improves rates of overall survival and durable stable disease. This disease stability is a valuable therapeutic goal for patients with mCRC who have received 2 prior lines of therapy. Regorafenib is not associated with high rates of myelosuppression. Side effects include hand-foot skin reaction. However, newer dosing strategies, such as those established by the ReDOS clinical trial[4] (discussed in the next article), provide an opportunity to optimize dosing and improve tolerability for patients. Regorafenib is a useful drug that can lead to long durations of stable disease.

The international, phase 3 IMblaze370 study (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma) evaluated cobimetinib and atezolizumab in patients with metastatic colorectal adenocarcinoma.[5]

Regorafenib was used as the standard of care in the comparator arm because it is approved globally in this treatment setting. The primary endpoint of overall survival did not significantly differ among any of the treatment groups. The median overall survival was 8.87 months with atezolizumab plus cobimetinib, 7.10 months with atezolizumab monotherapy, and 8.51 months with regorafenib. The median progression-free survival was also similar, at 1.91 months, 1.94 months, and 2.00 months, respectively. Among patients in the regorafenib arm, survival exceeded the protocol assumption of 6.4 months, which was based on data from the CORRECT study.[2,5]

Trifluridine/Tipiracil

Trifluridine/tipiracil is a novel compound indicated for the treatment of patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biologic therapy, and, if *RAS* wild-type, an anti-EGFR therapy.[6] The mechanism of action of trifluridine/tipiracil is unique. The thymidine-based nucleoside analogue trifluridine is an oral cousin of the chemotherapeutic agent 5-fluorouracil (5-FU) and is formulated together with the thymidine phosphorylase inhibitor tipiracil. Following uptake into cancer cells, trifluridine is incorporated into DNA, and interferes with DNA synthesis and inhibits cell proliferation. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. Trifluridine/tipiracil does not induce tumor regression, but as shown

in clinical trials, it can stabilize disease.[7,8] Importantly, this disease stabilization translates to significantly prolonged progression-free survival and overall survival, particularly in elderly patients with comorbidities and an ECOG performance status of 2.[7,8] Therefore, trifluridine/tipiracil can be an option for patients with these characteristics. The clinical trials 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) and TERRA (Study of TAS-102 in Patients With Metastatic Colorectal Cancer in Asia) established the efficacy and safety of trifluridine/tipiracil in mCRC.

The double-blind, randomized, phase 3 RECOURSE trial evaluated the safety and efficacy of trifluridine/tipiracil.[7] A total of 800 patients with refractory mCRC were enrolled. All patients had received at least 2 prior standard treatments (including adjuvant chemotherapy).

Patients were randomly assigned to treatment with trifluridine/tipiracil (35 mg/m^2 twice daily for 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period) or placebo.[7] Treatment cycles were repeated up to 4 times, and patients in both arms received best supportive care. Patients were stratified by *KRAS* status, the time from first diagnosis of metastasis, and geographic region. At baseline, the median patient age was 63 years, and 61% were male. ECOG performance status was 0 in 56% and 1 in 44%. The majority of patients (61%) had received 4 or more prior therapies.

The primary endpoint, 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; Figure 5).[7] The benefit in overall survival observed with trifluridine/tipiracil was evident in nearly all prespecified patient subgroups.

The secondary endpoint of median progression-free survival was 2.0 months with trifluridine/tipiracil vs 1.7 months with placebo (HR, 0.48; 95% CI, 0.41-0.57; *P*<.001).[7] The overall response rate was low in both arms (1.6% vs 0.4%, respectively; *P*=.29). The disease control rate—including patients with stable disease—was 44% in the trifluridine/tipiracil arm vs 16% in the placebo arm (*P*<.001). Trifluridine/tipiracil was also associated with a significant delay in the worsening of ECOG performance status from baseline levels of 0 or 1 to 2 or higher (5.7 months with trifluridine/tipiracil vs 4.0 months with placebo; HR, 0.66; 95% CI, 0.56-0.78; *P*<.001).

There is a high risk for myelosuppression among patients treated with trifluridine/tipiracil. Nausea is another notable side effect. Grade 3 or higher AEs were more common with trifluridine/tipiracil vs placebo. These events included neutropenia (38% vs 0%), anemia (18% vs 3%), and thrombocytopenia (5% vs <1%).[7] Patients in the trifluridine/tipiracil arm were also more likely to develop grade 3 or higher nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%).

The TERRA study was a confirmatory, randomized, double-blind, placebo-controlled phase 3 trial that assessed trifluridine/tipiracil in an Asian population with mCRC.[9] Patients were randomly assigned to treatment with trifluridine/tipiracil (n=271) or placebo (n=135) in a similar design as the RECOURSE study. Compared with the RECOURSE study, patients in the TERRA trial had lower exposure to biologic agents.

The median overall survival was 7.8 months with trifluridine/tipiracil vs 7.1 months with placebo.[9] This difference translated to a significantly lower risk of death with trifluridine/tipiracil vs placebo (HR, 0.79; 95% CI, 0.62-0.99; log-rank *P*=.035). The incidence of serious AEs was similar in both arms.

There is some evidence suggesting that when trifluridine/tipiracil is administered with bevacizumab, efficacy may be improved. In a retrospective analysis of 60 patients treated with trifluridine/tipiracil plus bevacizumab, this combination seemed to prolong progression-free survival compared with a matched cohort of patients treated with trifluridine/tipiracil alone.[10] The ongoing phase 2/3 TRUSTY study (Trifluridine/Tipiracil in Second-Line Study) is comparing trifluridine/tipiracil plus bevacizumab vs irinotecan/5-FU plus bevacizumab as second-line treatment in patients with mCRC that had progressed during or following first-line oxaliplatin-based chemotherapy.[11]

Anti-EGFR Agents

The anti-EGFR agents have different patterns of use in the United States and Europe. In the United States, clinicians tend to save EGFR-targeted therapies for later lines, particularly in patients with the left-sided, *RAS* wild-type, or *BRAF* wild-type disease subtypes. When an anti-EGFR agent is used in earlier lines of treatment, it can be used again to rechallenge the patient in later lines. Some ongoing clinical trials are investigating the benefit of this strategy. The emergence of resistance can be detected with newer technologies, such as measurement of cell-free DNA and other circulating biomarkers, to help predict which patients will not respond to rechallenge with EGFR-targeted therapy.

Selecting Patients for Third-Line Treatment

Patient selection is extremely important when considering the use of regorafenib or trifluridine/tipiracil. An example of a patient who is a poor candidate for either treatment is one who is hospitalized and has a worsening performance status, and for whom hospice care is being considered. These agents will not help that type of patient recover.
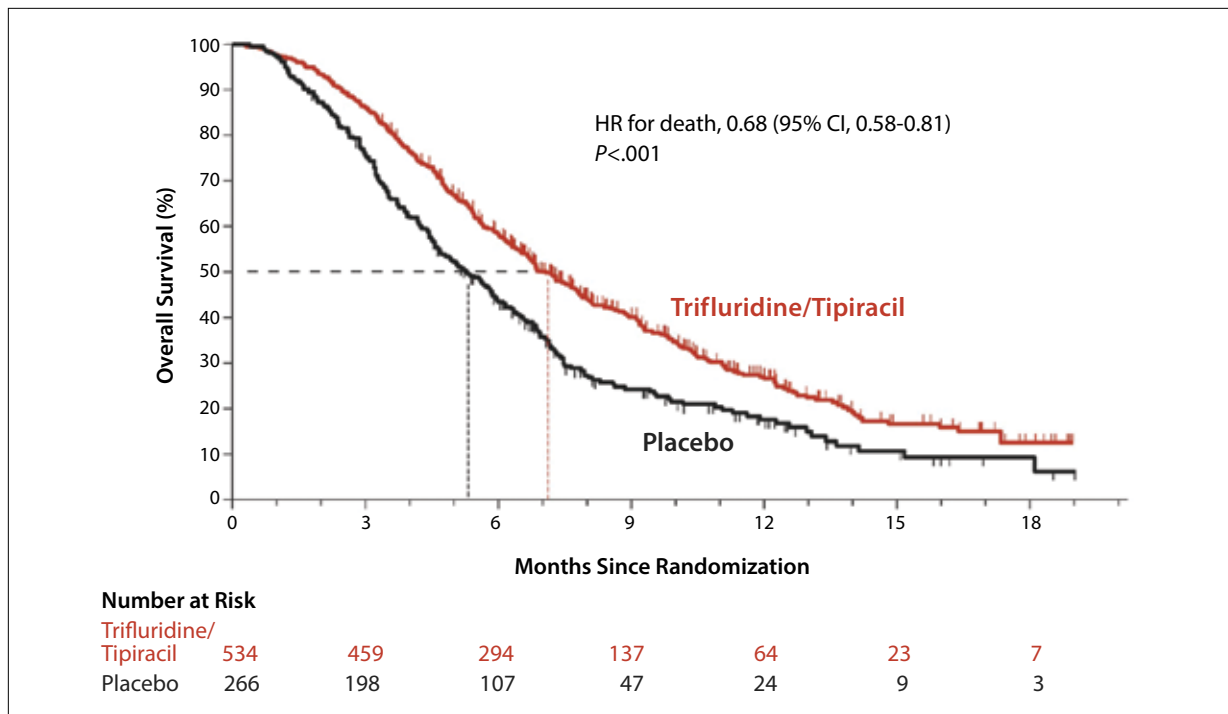
Figure 5. Overall survival was improved with trifluridine/tipiracil vs placebo in the phase 3 RECOURSE trial. HR, hazard ratio; RECOURSE, Randomized, Double-Blind, Phase 3 Study of TAS-102 Plus Best Supportive Care [BSC] Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies. Adapted from Mayer RJ et al. *N Engl J Med.* 2015;372(20):1909-1919.[7]

Instead, studies confirm that these treatments should be used earlier in the treatment course in patients who are in much better shape. Clinical data have shown that the efficacy of regorafenib is most apparent in patients with a good performance status (an ECOG performance status of 0 or 1). For example, an exploratory analysis of the CONSIGN study (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy) found that patients with progression-free survival exceeding 4 months were more likely to have characteristics such as an ECOG performance status of 0, no liver metastases, and a longer time since diagnosis of metastatic disease.[12]

When considering sequencing of therapies from the first line through later lines, the clinician must integrate all of the patient's variables and characteristics into treatment decisions. Factors such as age, comorbidities, personal preferences, and mutational status (including targets such as microsatellite instability, *RAS*, *BRAF*, *NTRK*, and *HER2*) are important. Tumor location is less relevant for regorafenib and trifluridine/tipiracil, but more important for anti-EGFR agents. It is essential to assess these factors in the beginning of treatment, so that they can inform treatment selection from the first line through later lines. Additionally, many of these factors are prognostic and/or predictive in nature, which can also increase their utility.

Real-World Evidence for the Use of Third-Line Targeted Therapies

There is ample real-world evidence to guide clinical decision-making in metastatic colorectal cancer. Real-world studies and expanded-access trials continue to support the efficacy of regorafenib and trifluridine/tipiracil, and have further increased knowledge on the use of these agents. It is possible to optimize the dosing schedule for regorafenib.

The CORRELATE Study

The CORRELATE study (Safety and Effectiveness of Regorafenib in Routine Clinical Practice Settings) was a prospective, observational cohort study that evaluated the safety and efficacy of regorafenib in an unselected, real-world population of patients with mCRC who were treated in routine clinical practice settings.[13,14] The study enrolled 1037 patients with mCRC throughout Europe, Asia, and Latin America. These patients had received previous treatment with other approved therapies, or were not considered candidates for them. Regorafenib was selected by their treating physician.

The primary objective of the CORRELATE study was to evaluate the safety of regorafenib in real-world practice, as evidenced by treatment-emergent AEs reported during treatment through 30 days afterward.[13,14] As a secondary objective, efficacy associated with regorafenib was assessed

by overall survival, progression-free survival, and disease control rate. The final analysis cut-off date was December 15, 2017.

The median patient age was 65 years, and 61% of patients were male. Notably, this age is typical of patients with mCRC, and was slightly older than the patient populations in the phase 3 trials of regorafenib. The primary tumor site was the colon in 70% of patients, the rectum in 28%, and the colon and rectum in 2%. Most patients (87%) had an ECOG performance status of 0 or 1. This was a relatively heavily pretreated group, with a median of 3 prior therapies, and 39% had received at least 4 prior systemic treatments.

The regorafenib dose was initially 160 mg in 57% of patients, 120 mg in 30%, and 80 mg or lower in 12%.[13,14] Patients who initiated regorafenib at the lowest dose category were more likely to be older and Asian, and to have a worse ECOG performance status. The dose was reduced at least once in 40% of patients. Dose reductions were more common among patients who initiated treatment at the highest dose (47% with 160 mg, 34% with 120 mg, and 22% with 80 mg). Reasons for treatment discontinuation included radiologic disease progression in 49% and regorafenib-related treatment-emergent AEs in 19%.

The incidence and severity of treatment-emergent AEs in the CORRELATE trial were generally consistent with the known safety profile of regorafenib.[13,14] The most frequent all-grade treatment-emergent AEs considered related to regorafenib were fatigue (41%), hand-foot skin reaction (26%), diarrhea (19%), mucositis (15%), hypertension (14%), and anorexia (13%). A total of 36% of patients developed a grade 3 or higher treatment-emergent AE that was related to regorafenib, most frequently fatigue (9%), hand-foot skin reaction (7%), and hypertension (6%).

Despite the different regorafenib dosing schedules used in CORRELATE, the efficacy was consistent with previous reports. The median overall survival was 7.7 months (95% CI, 7.2-8.3), and the estimated rate of 1-year overall survival was 34%.[14] The median progression-free survival was 2.9 months (95% CI, 2.8-3.0), and the estimated rate of 6-month progression-free survival was 21% (Figure 6).

The CORECT Registry

The CORECT registry, from the Czech Republic, is a noninterventional postmarketing database for patients with CRC who were treated with targeted agents in clinical practice. A total of 148 patients from 20 oncology centers throughout the country were included in this registry.[15]

At the time that treatment with regorafenib was started, nearly all patients were fully active or slightly restricted in physical activity.[15] The median progression-free survival was 3.5 months. At 1 year, 44.6% of patients were alive, and the median overall survival was 9.3 months. Four patients achieved a partial response, and 51 had stable disease. The most common AEs reported in the registry were skin toxicity (5.4%) and fatigue (2.0%).

The PRECONNECT Study

In October 2016, the phase 3b PRECONNECT study (An Open-Label Early Access Phase IIIb Study of Trifluridine/Tipiracil [S 95005/TAS-102] in Patients With a Pretreated Metastatic Colorectal Cancer) was initiated among patients with mCRC to assess the safety and efficacy of trifluridine/tipiracil in daily practice.[16] The study enrolled 462 patients from 10 countries who had received at least 1 dose of trifluridine/tipiracil. The patients' median age was 64 years (range, 28-87), and approximately 47% were ages 65 years or older. Approximately 64% were male. Among the 450 patients who were evaluable for ECOG performance status, the score was 0 in 46% and 1 in 54%. A *RAS* mutation was present in 52.2% of the patients. The primary site of disease was the left side in 62.8% of patients, the right side in 24.5%, and not specified in 12.8%. At baseline, prior treatments included fluoropyrimidine, oxaliplatin, and/or irinotecan in 94%; an anti-VEGF agent in 83%; an anti-EGFR agent in 41%; and regorafenib in 35%.

At the study cutoff date, 29 patients remained on treatment (6.2%).[16] The primary cause of study withdrawal (77.4%) was progressive disease. An AE led 6.7% of patients to stop study treatment. The median duration of trifluridine/tipiracil was 12.9 weeks (range, 2-48), and patients completed a median of 3 cycles (range, 1-12). The median relative dose intensity was 89%. A reduction in the dose of trifluridine/tipiracil was required by 8% of patients. Neutropenia was the primary cause, leading 2.8% of patients to reduce the dose. Deterioration of the ECOG performance status to 2 or higher occurred at a median of 8.7 months.

Drug-related AEs were reported in 74.5%, and most frequently consisted of neutropenia (49.5%), nausea (27.7%), and diarrhea (20.6%).[16] Grade 3 or higher drug-related AEs were reported in 48.6% of patients. These AEs were primarily hematologic, and included neutropenia (38%), anemia (7.1%), febrile neutropenia (1.7%), and thrombocytopenia (1.3%). The most common nonhematologic grade 3 or higher AEs were diarrhea (3.5%) and fatigue (2.2%).

A total of 414 patients treated with trifluridine/tipiracil in the PRECONNECT trial underwent at least 1 postbaseline tumor evaluation. In these patients, the median progression-free survival was 3.2 months (95% CI, 2.8-3.4), and the disease control rate was 41.1%
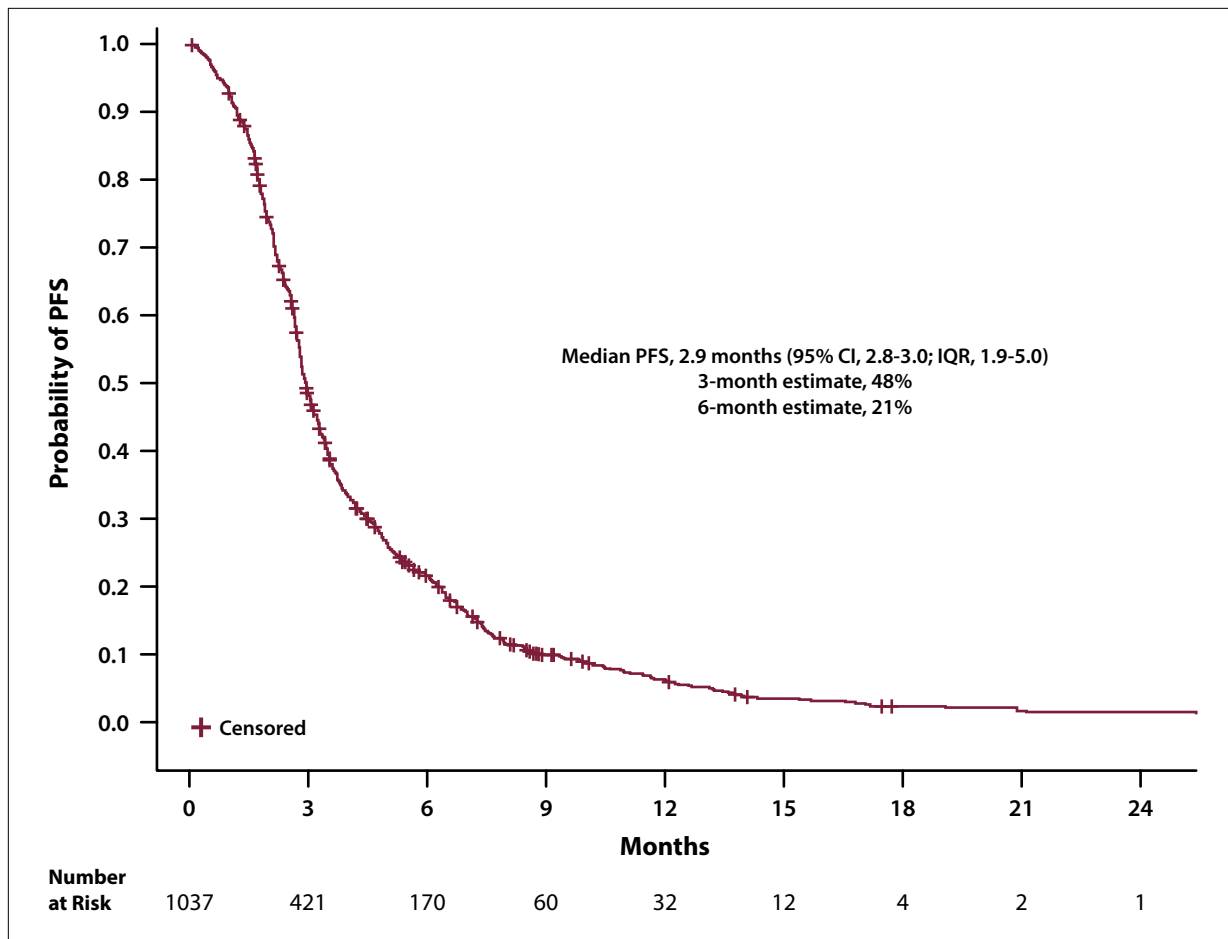
Figure 6. Progression-free survival in CORRELATE, a prospective, observational cohort study that evaluated the safety and efficacy of regorafenib in an unselected, real-world population of patients with mCRC who were treated in routine clinical practice settings. CORRELATE, Safety and Effectiveness of Regorafenib in Routine Clinical Practice Settings; IQR, interquartile range; PFS, progression-free survival. Adapted from Ducreux M et al. *Eur J Cancer.* 2019;123:146-154.[14]

(95% CI, 36.3-46.0).[16] At the time of data cut-off, 91.3% of patients were alive, and the median overall survival had not been reached.

Lessons Learned During the COVID-19 Pandemic

Our management plan now incorporates new lessons learned during the current global COVID-19 pandemic caused by the SARS-CoV-2 virus. In partnership with the Colorectal Cancer Alliance and the Otto J Ruesch Center for the Cure of Gastrointestinal Cancers at the Georgetown University Lombardi Comprehensive Cancer Center, my colleagues Drs Ronit Yarden and Benjamin Weinberg and I recently published a set of guidelines and recommendations for the management of colorectal cancer during the COVID-19 pandemic.[17]

One of the primary guiding principles underlying these recommendations is to avoid unnecessary clinic and hospital exposure.[17] Every trip to the clinic or hospital poses an inherent risk for exposure, and clinicians must do everything possible to reduce this risk. We have learned that telemedicine permits the remote management of patients who are receiving oral therapies. In this regard, oral therapies such as regorafenib and trifluridine/tipiracil are choices as a bridge away from traditional intravenous chemotherapy. However, the choice of an oral therapy should also take into consideration the risk of myelosuppression. There is a need for close follow-up, even on a weekly basis, of patients during treatment with these agents. Follow-up may include laboratory studies, for example to assess for myelosuppression with trifluridine/tipiracil or for liver function abnormalities with regorafenib. In addition, it is important to interact with the patient in order to identify side effects, such as hand-foot skin reaction. This follow-up can be accomplished remotely with televisits, which also allow the opportunity

to visually assess the patient's appearance. It is increasingly likely that clinicians will rely on televisits as part of an everyday management strategy, even after this pandemic. We and other researchers are developing tools to help remotely communicate with patients to avoid the need for hospital visits.

A related factor is the recommendation to avoid severe (grade 3 or 4) drug-related AEs, which may require the patient to enter the emergency room or hospital.[17] These severe AEs may include nausea, vomiting, diarrhea, mucositis, and febrile neutropenia. Careful monitoring of kidney and liver function can help predict risk. Another mitigation strategy may be to dose-reduce intensive regimens, particularly during the first few cycles. Omitting the bolus 5-FU portion from the typical regimens of folinic acid, 5-FU, and oxaliplatin (FOLFOX) or folinic acid, 5-FU, and irinotecan (FOLFIRI) may be an especially important modification in an effort to reduce severe myelosuppression, mucositis, and diarrhea.

Another consideration for managing patients with mCRC during the COVID-19 pandemic is to reduce their exposure to agents that are potentially myelosuppressive.[17] The use of myelosuppressive regimens, such as folinic acid, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) and trifluridine/tipiracil, is increasing. These agents are associated with a significant degree of grade 3 and 4 neutropenia and anemia. Because myelosuppression is associated with immunosuppression, it may increase vulnerability to infection in the event of exposure to SARS-CoV-2. It should be considered good practice to avoid these hematologic toxicities as much as possible, particularly because of their immunosuppressive impact. Skipping a single cycle of treatment may help avoid the need for medical management of an AE, particularly for agents with long half-lives (eg, bevacizumab). In the third-line setting, the choice between regorafenib and trifluridine/tipiracil should take into consideration that the latter is an oral cytotoxic drug and therefore associated with the potential for grade 3/4 myelosuppressive AEs, which may cause immunosuppression.

The ASCO Post also published recommendations from Drs Axel Grothey, Johanna C. Bendell, and Scott Kopetz.[18] These experts agree that the risk of myelosuppression should be mitigated through selection of therapy. It is preferable to modify, rather than delay, treatment. Telemedicine will likely remain an important component of management, even after this pandemic ends.

Disclosure

Dr Marshall is a speaker and consultant for Amgen, Bayer, Taiho, and Merck. He also works with Caris and Indivumed.

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The Importance of Keeping Patients With Metastatic Colorectal Cancer on Treatment Through the Management of Adverse Events

Axel Grothey, MD

Director, GI Cancer Research
West Cancer Center and Research Institute
OneOncology
Germantown, Tennessee

The goal of palliative therapies is to extend the duration of life, while maintaining quality of life for as long as possible. To meet this goal, it is necessary to ensure that all potentially active agents are available to all patients. The approach to management of mCRC therefore reflects a continuum of care. Patients are not only switched from one line of therapy to another, but therapy is individualized according to the patient's molecular markers, tolerance to therapy, and the previous side effects that developed. The goal is to keep patients on life-prolonging treatment while managing AEs. Providing patients with proactive education about potential side effects can help mitigate severe toxicities. Additionally, providing patients a chemo-free interval can help manage their quality of life.

Managing Adverse Events Associated With Chemotherapy and Biologic Agents

Every patient has a unique risk of developing side effects. There are patients who can tolerate even a triplet chemotherapy regimen, such as FOLFOXIRI, without any major toxicities. Other patients develop severe nausea and vomiting, the more dominant side effects, as well as others such as fatigue, diarrhea, and neurotoxicity.

When speaking with my patients about what to expect during treatment with chemotherapy—for example, FOLFOX or FOLFIRI combined with a biologic agent in the first-line setting—I highlight the potential common side effects. The most frequent side effects associated with chemotherapy are fatigue, diarrhea, and sometimes constipation. Other common side effects include alopecia, mucositis, and myelosuppression.

Some patients who receive irinotecan have a propensity to develop severe diarrhea early in the course of therapy. In my experience, diarrhea is not dependent on cumulative exposure to irinotecan. Instead, diarrhea either does or does not occur in a particular patient. When diarrhea does occur, severe cases can be seen as early as the first cycle of irinotecan treatment.

Neuropathy may become a concern, particularly with oxaliplatin-containing regimens. Oxaliplatin is associated with 2 distinct types of neurotoxicity syndromes. The first, a cold-induced sensory neuropathy, is common. It has an acute onset, and often manifests in the throat, esophagus, and palms of the hands. Although a transient phenomenon, it can cause pain when the patient swallows liquids and may markedly impair quality of life. Cold-induced sensory neuropathy often presents early during the course of treatment.[1]

The second type of neurotoxicity syndrome is a dose-limiting, cumulative sensory neurotoxicity. It tends to occur after cumulative doses exceeding 780 mg/m^2 to 850 mg/m^2. This cumulative sensory neuropathy manifests as dysesthesias and paresthesia of the extremities that generally persist between cycles and tend to increase in intensity with each dose. These symptoms can negatively affect quality of life, and may even be severe enough to prevent patients from participating in activities of daily living.[1]

Cold-induced sensory neuropathy has an early onset with oxaliplatin, and patients should be educated about the need to avoid exposure to cold. This event is different from the cumulative neurotoxicity that is associated with the duration of therapy. In clinical practice, I use no more than 8 cycles of first-line oxaliplatin-based therapy before I remove oxaliplatin from the regimen and initiate maintenance therapy. This strategy allows use of oxaliplatin later in the treatment course, by avoiding persistent neurotoxicity.

Another effect, referred to as the "coasting" phenomenon, has been reported with oxaliplatin.[2] In this delayed effect, after patients stop oxaliplatin, sensory neurotoxicity worsens before it improves. In some cases, this may be attributed to a treatment switch (eg, from FOLFOX plus bevacizumab as induction therapy to capecitabine/bevacizumab as maintenance therapy), causing patients to experience an overlap of side effects. As an example, a patient might experience neurotoxicity associated with oxaliplatin and hand-foot toxicity associated with capecitabine. Because both of

these effects manifest in the hands and feet, it is difficult to distinguish between them. The patient may presume that neurotoxicity may be worsening with capecitabine, when really it is a persistent effect from the previous treatment. Hand-foot syndrome associated with capecitabine typically begins as erythema of the hands and feet, and then progresses to pain and sensitivity in these extremities. This hand-foot syndrome is considered a dose-limiting toxicity of capecitabine, and can significantly impact quality of life. Treatment interruption or dose reduction are the primary means of management.[3]

Skin rashes tend to occur with the EGFR-targeted antibodies cetuximab and panitumumab.[4] The most common is a papulopustular skin rash that can impact quality of life and adherence to therapy. The incidence and severity of skin toxicities seems to be similar with cetuximab and panitumumab, and severity is increased when these agents are used together with bevacizumab.[5,6] The National Comprehensive Cancer Network (NCCN) strongly advises against the concurrent use of these agents.[4] Clinical data in mCRC suggests there is a positive correlation between the presence and severity of rash and survival outcomes.[7,8]

With all of these treatments, there is also a high risk for infectious complications. This risk can be lowered, however, through implementation of neutropenia-mitigating modifications of chemotherapy. These mitigations might include omitting the bolus 5-FU from the FOLFOX and FOLFIRI regimens, or switching to a capecitabine-based regimen, such as capecitabine plus oxaliplatin, with a much lower risk of neutropenia.

Strategies to Manage Regorafenib-Associated Adverse Events

When considering the AEs associated with regorafenib, it is important to reiterate that this agent should not be used too late in the lines of therapy. Regorafenib will not have a beneficial effect in patients who have deteriorated, and who have a poor performance status and progressive disease. Clinical studies of regorafenib did not enroll patients with an ECOG performance status of 2 or higher.

The clinical studies of regorafenib showed that the side effects—primarily, fatigue, hand-foot skin reaction, and skin rash—generally occur early in treatment. For example, in the initial phase 3 trials CORRECT and CONCUR, patients first presented for a follow-up visit 2 weeks after starting the drug.[9,10] It became clear that this was too late. Patients had already developed a significant degree of toxicity, even at this early time point. It is therefore necessary to see patients after just 1 week of therapy. This follow-up protocol provides a perfect application for the use of telemedicine, so that patients do not have to come into the clinic. Via telemedicine,

clinicians can assess the patients for the side effects that are particularly pertinent to regorafenib.

The hand-foot skin reaction that occurs with regorafenib is different from the hand-foot syndrome associated with capecitabine.[11] Hand-foot skin reaction is an inflammatory reaction, which manifests mainly as peeling or blisters on the hands and soles of the feet. This reaction can be particularly painful, and has the potential to impair quality of life and activities of daily living. With regorafenib, hand-foot skin reaction is an early effect of treatment, whereas the hand-foot syndrome associated with capecitabine occurs over time (tending to maximally occur during the second or third treatment cycle). In a meta-analysis of regorafenib trials across different tumor types, hand-foot skin reaction occurred at a rate of 61% overall, with grade 3 reactions reported in 20%.[12] All-grade cases were reported in 71% of patients with renal cell carcinoma, 60% of those with a gastrointestinal stromal tumor, and 47% of those with mCRC. Interestingly, evidence from clinical studies supports the notion that those patients who develop hand-foot skin reactions with regorafenib seem to experience a better outcome, including prolonged overall survival.[13] This is a silver lining that can be communicated to patients who experience this side effect.

Since the initial clinical trials were conducted, knowledge has improved regarding dosing strategies for regorafenib. It is now recognized that the side effects of regorafenib arise early, within the first 2 weeks of therapy. Additionally, as a cytostatic agent, the duration of regorafenib therapy is important. The goal is to keep patients on this agent for as long as possible. Cytostatic agents will work only for as long as they are administered. It is critical to optimize the duration of therapy, by mitigating and preventing side effects, in order to achieve the best outcomes.

The randomized phase 2 ReDOS trial evaluated different dosing strategies for regorafenib as the main intervention (Figure 7).[14] The aim of ReDOS was to assess whether regorafenib-associated toxicities could be minimized with a different dosing regimen, with the additional benefit of extending the duration of therapy. In ReDOS, patients were randomly assigned to treatment with the standard dosing schedule of regorafenib or an escalated dosing schedule. Patients in the standard arm received the approved dose of 160 mg administered as 4 tablets once daily. With the escalated dosing schedule, regorafenib was initiated at 80 mg, administered as 2 tablets daily, in the first week. Patients were assessed from week to week to determine whether the dose could be increased over time. When appropriate, the dose was increased to 120 mg daily during week 2, and potentially up to the standard dose of 160 mg daily during week 3. The dose during the
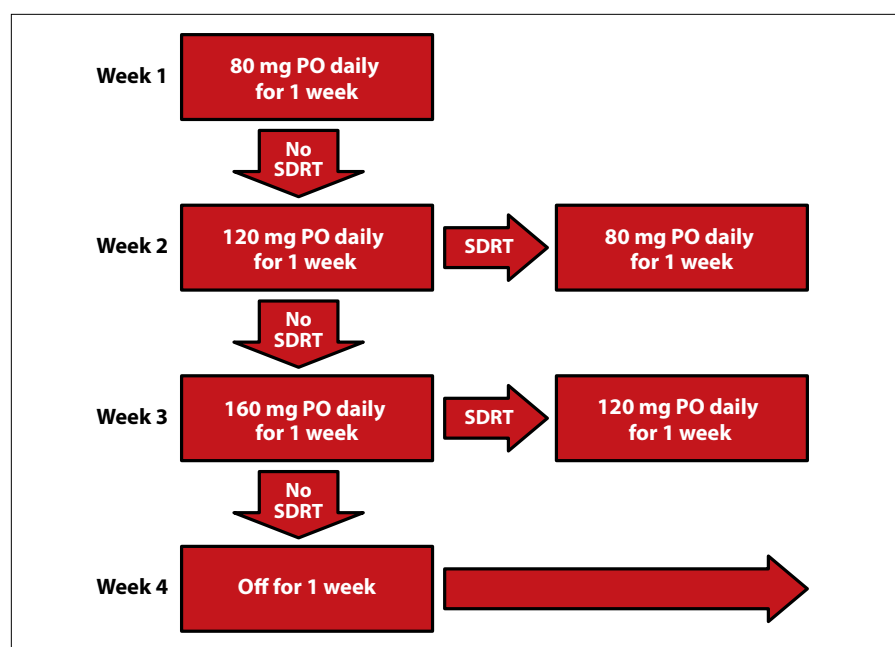
Figure 7. An incremental dose-escalation schedule for regorafenib can minimize toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2015;13(8):514-517.[18]

second cycle was determined by the dose that was tolerated during the first cycle. In both arms, treatment was continued for 3 weeks on and 1 week off. At baseline, the patients' median age was 61.5 years, and 63% had an ECOG performance status of 1.

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*=.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. Importantly, the improved rates of stable disease that were achieved in the escalated-dosing arm translated to prolonged overall survival. The median overall survival was 9.8 months in the escalated-dosing arm vs 6.0 months in the standard-dosing arm, although this difference did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank *P*=.12; Figure 8).[14] The findings from the ReDOS study have had significant practice-changing implications, and have the potential to drive how regorafenib is now administered in the clinic.[15]

Strategies to Manage Adverse Events Associated With Trifluridine/Tipiracil

Trifluridine/tipiracil has a different AE profile from regorafenib. For trifluridine/tipiracil, the primary AEs reported in clinical trials were hematologic toxicities. In the phase 3 RECOURSE study, AEs of grade 3 or higher that were more frequent in the trifluridine/tipiracil arm

compared with the placebo arm included neutropenia (38% vs 0%), anemia (18% vs 3%), and thrombocytopenia (5% vs <1%).[16] Likewise, hematologic toxicities were reported in the phase 3b PRECONNECT study. In this study, neutropenia was the most common reason for dose reduction (3.4%). Neutropenia was also the most frequently reported grade 3 or higher AE (39.1%), followed by anemia (9.8%) and asthenia/fatigue (5.0%).[17] The median time to deterioration in ECOG performance status was 8.9 months (Figure 9).

The neutropenia reported with trifluridine/tipiracil is primarily asymptomatic; few patients develop febrile neutropenia. That being said, in the era of a global pandemic, such as the current one caused by the SARS-CoV-2 virus, it is necessary to avoid any risk of neutropenia and associated potential for immunosuppression. These factors may influence the choice of which drugs should be administered first.

Sequencing Regorafenib and Trifluridine/Tipiracil

The optimal sequencing of regorafenib and trifluridine/tipiracil is not yet established. I tend to administer regorafenib first, for several reasons. First, by the third-line setting, patients have received various lines of chemotherapy. It can be beneficial to provide a chemo-free interval, and the biologically targeted mechanism of action with regorafenib is a good alternative. Patients who have exhausted their bone marrow reserve with chemotherapy regimens might benefit from a chemo-free interval. Second, it is important to consider exposing the cancer to a different
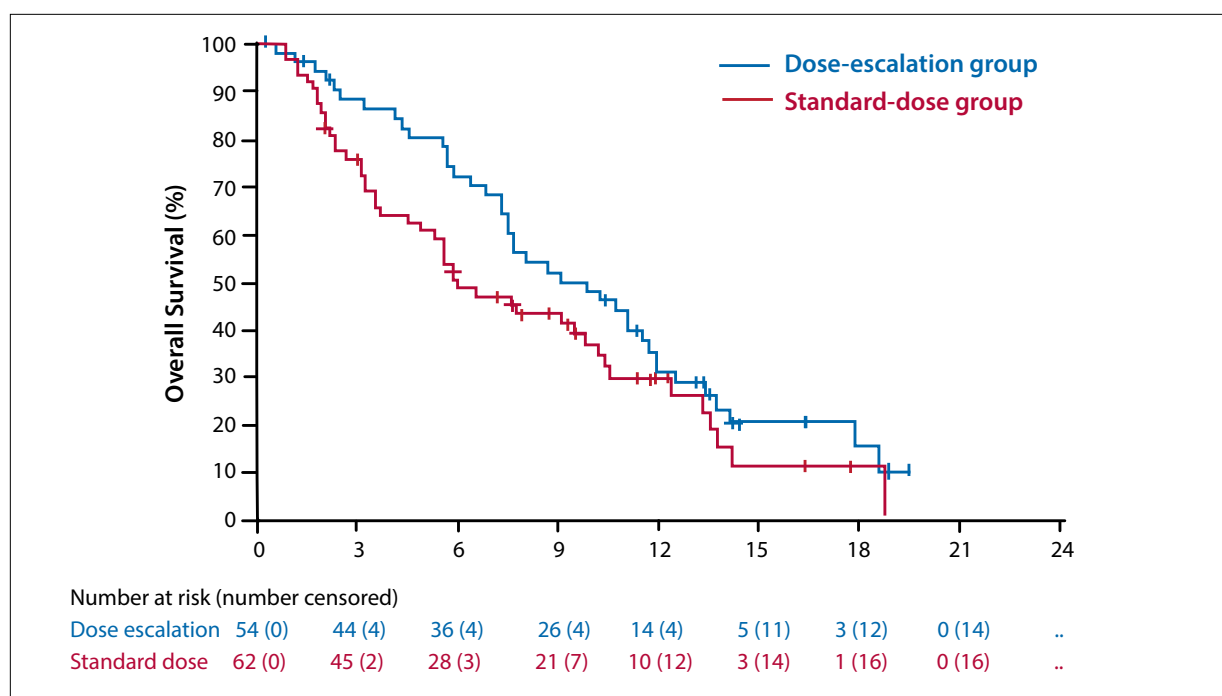
Figure 8. Overall survival in the randomized phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen. In the dose-escalation arm, regorafenib was initiated at 80 mg/day, and was increased weekly up to 160 mg/day in the absence of significant drug-related toxicities. Patients in the standard-dose arm received regorafenib at 160 mg/day. ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab TS et al. *Lancet Oncol.* 2019;20(8):1070-1082.[14]

treatment approach with an active agent like regorafenib. Third, the use of chemotherapy after regorafenib has demonstrated efficacy. Trifluridine/tipiracil is a chemotherapeutic agent that can work after treatment with regorafenib. In the phase 3 RECOURSE study of trifluridine/tipiracil, 18% of the population had received prior regorafenib, in addition to other systemic therapies.[16] An analysis of the overall survival benefit showed that trifluridine/tipiracil was similarly effective regardless of whether the patient received prior treatment with regorafenib (HR, 0.69; 95% CI, 0.45-1.05) or did not (HR, 0.69; 95% CI, 0.57-0.83).

Clinical experience shows that regorafenib is less likely to prolong survival in patients with an ECOG performance status of 2 or higher. These patients should not receive regorafenib. However, these patients may be candidates for trifluridine/tipiracil, which has a subjectively less-taxing side effect profile. My concern is that if trifluridine/tipiracil is used first, afterward the patient's performance status may deteriorate to the extent that regorafenib is no longer an option. This approach could therefore interfere with the principle of exposing patients to all active agents to the greatest extent possible throughout all lines of therapy.

It is possible to mitigate the side effects of regorafenib, thereby allowing patients to stay on treatment longer. Extending the duration of therapy is critical in the overall management of patients, as a component of the continuum of care and to maintain quality of life. Outcome will be improved for patients throughout all lines of therapy, including later lines of treatment with regorafenib and trifluridine/tipiracil.

Disclosure

Dr Grothey's institution has received honoraria for consulting activities from Bayer, Roche/Genentech, Array/Pfizer, Boston Biomedical, Daiichi, OBI Pharmaceuticals, and Caris. He has received travel support from Bayer, Roche/Genentech, and Array.

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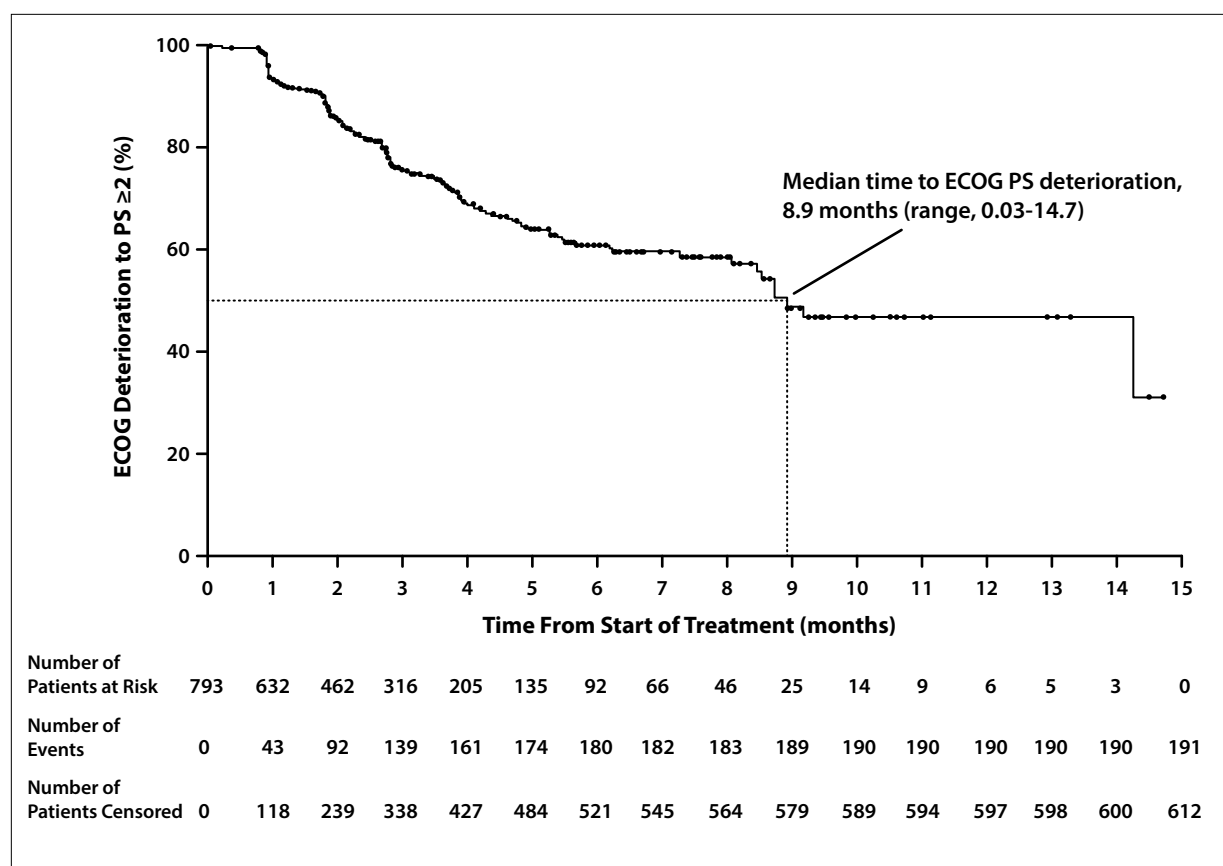
Figure 9. The median time to an ECOG performance status of 2 or higher among patients treated with trifluridine/tipiracil in the phase 3b PRECONNECT study. The study censored 2 patients from the analysis who received another anticancer therapy after withdrawal from the study drug, and who lacked a postbaseline efficacy evaluation. The analysis included 24 patients who lacked baseline ECOG performance status data, but had data collected at subsequent visits. ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; PRECONNECT, A Study of Trifluridine/Tipiracil [Also Known as S 95005 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.[17]

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How to Incorporate a Chemo-Free Interval Into the Management of Metastatic Colorectal Cancer: Discussion

Axel Grothey, MD

Director, GI Cancer Research
West Cancer Center and Research Institute
OneOncology
Germantown, Tennessee

John L. Marshall, MD

Chief, Division of Hematology/Oncology
Medstar Georgetown University Hospital
Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Director, Otto J. Ruesch Center for the Cure of Gastrointestinal Cancers
Georgetown Lombardi Comprehensive Cancer Center
Georgetown University
Washington, DC

Axel Grothey, MD For most patients, when I start chemotherapy, I prefer an induction/maintenance approach. I like the combination of a fluoropyrimidine plus bevacizumab, which I believe is a very strong regimen. There are some patients who do not want to receive treatment for a long duration and who want to avoid maintenance therapy. However, the majority of patients will commit to the idea that as long as there is cancer to treat, they will be receiving some sort of therapy.

John L. Marshall, MD Agreed. I take a similar approach, starting with a doublet of capecitabine and bevacizumab, and continuing maintenance with bevacizumab. However, after 6 or 9 months, if the disease remains stable, I might reduce or even skip a bevacizumab dose to try to further minimize treatment while still maintaining the response. But this is something I do several months out, not right away.

Axel Grothey, MD That is a great point. I tell my patients that we need to find the least amount of treatment that is able to control their disease. This is the "art" of oncology—instead of being locked into a dosing strategy, you can see where and when it is possible to further de-escalate the dose or extend the treatment interval. I am liberal with giving patients time off treatment during holidays or family events. The more we know about the biology of the cancer, and in cases where the treatment is leading to controlled, low-volume disease, the more liberal we can be with dose modifications.

John L. Marshall, MD In the United States, there is a great deal of concern about deviating from guidelines, standard doses, and lines of therapy, particularly with regard to reimbursement. I understand that concern. Deviation from the standard, even using a ReDOS schedule[1] or modified doses of capecitabine, usually leads to a follow-up phone call from a pharmacy. Optimizing treatment strategies can increase the workload for the practice overall because of insurance oversight.

Axel Grothey, MD Sometimes when my patients treated with capecitabine are having a difficult time with hand-foot syndrome or diarrhea, I modify the regimen to use it Monday to Friday with the weekends off, while keeping the same dosage. In my experience, this is much better tolerated than the strategy of 2 weeks on and 1 week off. This approach is similar to what we do in rectal cancer, and I find that the rectal cancer dosing approach tends to be much better tolerated.

John L. Marshall, MD I find using a continuous dose, or more typically giving the treatment Monday through Friday weekly, to be the most tolerable and effective schedule. I start most patients at 1000 mg to 1500 mg twice daily Monday through Friday, and follow them closely for cumulative toxicity. Of course, this strategy is for patients with normal renal function.

Axel Grothey, MD There are some patients who have their cancer controlled on an irinotecan-based therapy

(eg, FOLFIRI-bevacizumab). When there is long-term use of this therapy, do you ever increase treatment intervals for 2 to 3 weeks?

John L. Marshall, MD I do. Of course, COVID-19 has taught us that this is probably a good idea. It is a gentler approach, particularly for irinotecan, and not much benefit is lost.

Axel Grothey, MD Yes, I completely agree. This is also something that I hope we can maintain after the COVID-19 pandemic. When you look at all the recommendations that arose from the NCCN Colorectal Cancer Task Force for COVID-19, many are self-evident and should have been implemented earlier.[2] For example, telemedicine is a perfect tool for monitoring toxicity with regorafenib. Deleting the bolus 5-FU is another long overdue recommendation; I do not think that bolus 5-FU should be in the armamentarium anywhere. Finally, switching to oral medicines and reducing exposure to healthcare facilities are important strategies that should be pursued. Hopefully, when the SARS-CoV-2 pandemic is over, clinicians can come together to determine which of these approaches had a positive effect on quality of life for our patients.

John L. Marshall, MD I am interested in increasing the application of ctDNA into daily practice. There are some data, but they must be expanded. We may gain some insights into how to use ctDNA in the management of stage IV patients. The use of ctDNA will likely help guide our therapy decisions.

Axel Grothey, MD Yes, I agree. ctDNA has a role in many mCRC settings, including in early-stage disease, and also as surveillance. Is it necessary to administer scans every 3 to 6 months to determine whether patients had a recurrence? Can we monitor treatment responses in the advanced setting for secondary resistance mechanisms that occur with treatment? There is much more to learn. I strongly believe that this research will change the way we practice oncology—not just colorectal cancer, but other diseases, too.

Disclosures

Dr Grothey's institution has received honoraria for consulting activities from Bayer, Roche/Genentech, Array/Pfizer, Boston Biomedical, Daiichi, OBI Pharmaceuticals, and Caris. He has received travel support from Bayer, Roche/Genentech, and Array. Dr Marshall is a speaker and consultant for Amgen, Bayer, Taiho, and Merck. He also works with Caris and Indivumed.

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Goals of Managing Patients With Metastatic Colorectal Cancer

- Most patients with metastatic colorectal cancer will receive different lines of therapy for the rest of their lives
- The primary treatment goals are to prolong survival while maintaining the best quality of life
- In the context of lifelong therapy, incorporating chemo-free treatment intervals is one strategy to help achieve these goals

Early Management of Metastatic Colorectal Cancer

- The recommended standard-of-care treatments consist of combination chemotherapy regimens, given with or without biologic agents
- In the real-world setting, patients generally reach a maximal response after 3 to 6 months of treatment
- After that, the chemotherapy agent may be withdrawn. The biologic agent is potentially continued as a maintenance treatment, although the benefit of maintenance therapy following first-line treatment is unclear
- In many cases, treatment after first-line therapy is stopped not because of side effects or disease progression, but rather to provide a break from chemotherapy

Third-Line Options for Metastatic Colorectal Cancer: Regorafenib

- Regorafenib is a multitargeted therapy, with a unique mechanism of action that inhibits multiple aspects of tumor biology and tumor-host interaction
- Regorafenib does not induce tumor regression, but clinical trials show it can stabilize disease.[1,2] Importantly, this disease stabilization translates to significantly prolonged progression-free and overall survival
- The patients best suited to receive regorafenib are those with a good performance status, and for whom stable disease is an acceptable option

1. Grothey A et al. Lancet. 2013;381(9863):303-312. 2. Li J et al. Lancet Oncol. 2015;16(6):619-629.

Third-Line Options for Metastatic Colorectal Cancer: Trifluridine/Tipiracil

- The thymidine-based nucleoside analog trifluridine is an oral cousin of the chemotherapeutic agent 5-FU and is formulated together with the thymidine phosphorylase inhibitor tipiracil
- Trifluridine/tipiracil does not induce tumor regression, but as shown in clinical trials, it can stabilize disease[1,2]
- This disease stabilization translates to significantly prolonged progression-free survival and overall survival, particularly in elderly patients with comorbidities and an ECOG performance status of 2

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil.
1. Mayer RJ et al. N Engl J Med. 2015;372(20):1909-1919. 2. Yoshino T et al. Lancet Oncol. 2012;13(10):993-1001.

When to Initiate Third-Line Therapy

- A fundamental mistake that oncologists make today is to withhold medicines with a known survival advantage until later lines of therapy
- Agents such as regorafenib and trifluridine/tipiracil are essentially ineffective in patients with a rapidly declining performance status
- It is necessary to implement these strategies earlier in the process, before the patient's performance status deteriorates
- Clinicians must monitor patients closely, in order to implement treatment with these agents at optimal time points

A Chemo-Free Interval

- A longer duration between frontline therapy with an anti-EGFR agent and rechallenge with an anti-EGFR agent corresponds to a better response to the latter treatment
- Clinicians should consider a chemo-free third line of treatment, particularly in patients with a very long interval before progression after first-line treatment and a relatively long interval after second-line treatment
- In this context, the best opportunity is the use of a multikinase inhibitor, such as regorafenib, which blocks several different pathways that are directly or indirectly related to activation of the microenvironment and angiogenesis

Helping Patients Stay on Treatment

- The goal of palliative therapies is to extend survival, while maintaining quality of life for as long as possible
- It is necessary to ensure that all potentially active agents are available to all patients. The approach to management of mCRC therefore reflects a continuum of care
- It is important to manage adverse events to keep patients on life-prolonging treatment
- Providing patients with proactive education about potential side effects can help mitigate severe toxicities

Data from Marshall JL et al. Colorectal Cancer. 2020;0(0):10.2217/crc-2020-0010.

Optimizing Use of Regorafenib

- Regorafenib should not be used too late in the lines of therapy. Regorafenib will not have a beneficial effect in patients who have deteriorated, and who have a poor performance status and progressive disease
- The side effects of regorafenib arise early, within the first 2 weeks of therapy
- As a cytostatic agent, the duration of regorafenib therapy is important. The goal is to keep patients on treatment for as long as possible
- An escalated dosing regimen can prolong treatment

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=.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

Data from Bekaii-Saab TS et al. Lancet Oncol. 2019;20(8):1070-1082.

Lessons Learned During the COVID-19 Pandemic

- Telemedicine permits the remote management of patients who are receiving oral therapies
- The choice of an oral therapy should take into consideration the risk of myelosuppression
- There is a need for close follow-up, even on a weekly basis, of patients during treatment with these agents. This follow-up can be accomplished remotely with televisits, which also allow the opportunity to visually assess the patient's appearance. It is increasingly likely that clinicians will rely on televisits as part of an everyday management strategy, even after the pandemic ends
- Researchers are developing tools to help remotely communicate with patients to avoid the need for hospital visits

Data from Marshall JL et al. Colorectal Cancer. 2020;0(0):10.2217/crc-2020-0010.

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