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Sequencing Beyond the Second-Line Setting in Metastatic Colorectal Cancer

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Abstract: The standard treatment for patients with metastatic colorectal cancer (mCRC) in the first- and second-line setting is generally chemotherapy, which can be augmented with vascular endothelial growth factor–targeted therapies and, for patients with *KRAS* wild-type status, epidermal growth factor receptor–targeted therapies. However, nearly all patients ultimately develop disease progression and require later lines of therapy. Traditionally, physicians recycled chemotherapy in the later lines, with many patients showing diminished or no response. However, the past several years have seen the introduction of 2 agents for patients with refractory mCRC entering the third-line setting. The multitargeted tyrosine kinase inhibitor regorafenib and the cytotoxic combination of trifluridine/tipiracil have demonstrated significant improvements in overall survival in patients with refractory mCRC. Although these agents do not seem to induce complete responses, they can lead to durable stable disease. Regorafenib and trifluridine/tipiracil differ in their safety profiles. Physicians and patients must be properly educated on how to recognize and mitigate adverse events. For regorafenib, a dose-escalating strategy improves tolerability without impacting efficacy. When sequencing these agents, physicians should consider patient characteristics, including comorbidities, prior adverse reactions to treatments, and overall performance status. Ongoing studies are further defining the role of regorafenib and trifluridine/tipiracil in the treatment of mCRC.

Options for Patients With Metastatic Colorectal Cancer Who Progress After Second-Line Therapy

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In the United States, an estimated 101,420 patients will be diagnosed with colon cancer and an additional 44,180 will be diagnosed with rectal cancer in 2019.[1] The number of annual diagnoses and deaths are shown in Figure 1.[2] Approximately 21% of patients with colorectal cancer (CRC) are diagnosed after the disease has metastasized.[2] Despite the availability of several effective therapies, most patients develop progressive disease that relapses multiple times and ultimately becomes refractory to treatment.

The overall prognosis of patients with metastatic colorectal cancer (mCRC) has benefited from the ever-widening number of therapies now approved for this disease. Today, the 5-year relative survival rate for patients with CRC is 64.5%, although this decreases to 13.8% among patients diagnosed when their disease has already metastasized.

First-Line and Second-Line Treatment Options for mCRC

Initial treatment options for mCRC consist of combination chemotherapy regimens, typically fluorouracil, irinotecan, and oxaliplatin. In the United States, it is common for the biologic agent bevacizumab, which targets the vascular endothelial growth factor (VEGF), to be combined with chemotherapy. However, despite these effective treatment options, the vast majority of patients relapse after initial therapy or develop progressive disease during first-line treatment.

Active agents are also available for the second-line treatment of mCRC. In the current era of molecular profiling, it is recommended that all patients undergo testing for microsatellite instability and for mutations in genes including *RAS* (*KRAS* and *NRAS*), *BRAF, HER2,* and *NTRK*. Approximately 40% of patients do not have mutations in either *RAS* or *BRAF*. These patients are classified as having *RAS/BRAF* wild-type tumors.[3] Notably, it is only patients with *RAS/BRAF* wild-type mCRC, and with a left-sided tumor, who seem to benefit from treatment with epidermal growth factor receptor (EGFR)-targeted agents, which include panitumumab and cetuximab.[4] In contrast, these agents have been shown to be largely ineffective, and even harmful, in patients with *RAS* mutations.[5]

In the United States, EGFR monoclonal antibodies are typically positioned beyond the first-line setting, after the patient has received VEGF-targeted therapy as front-line treatment. Some physicians opt to reserve EGFR inhibitors for the third-line setting, particularly because of their associated toxicities (namely, a common rash).[6] Another option is to implement anti-EGFR therapy in the first-line setting, and rely on VEGF-targeted agents in the second-line setting and beyond. Regardless, clinical data suggest that the sequence of VEGF- and EGFR-targeted therapies does not appear to impact their efficacy.[7-11]

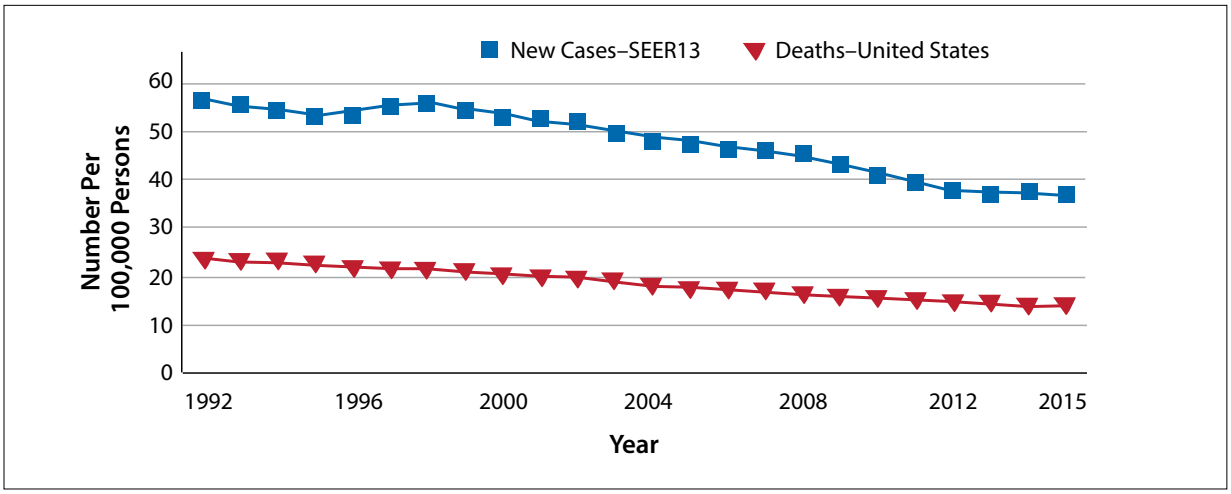

Figure 1. New cases and deaths from colorectal cancer in the United States. SEER, Surveillance, Epidemiology, and End Results Program. Adapted from Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed January 12, 2019.[2]

Selecting Later Lines of Therapy

By the time patients with mCRC reach their third line of treatment, they are usually well-known to their physician. It is well established whether their cancer is resectable, based on the tumor burden and location. Patients will generally have received fluorouracil-based chemotherapy (with oxaliplatin and irinotecan), VEGF-based therapy, and EGFR-targeted therapies (for those with left-sided *RAS* wild-type tumors). When patients with mCRC continue to experience disease progression after these systemic therapies, they are then considered to have refractory mCRC. Although the disease is incurable, there are several options even for these heavily pretreated patients.

In my clinic, this transition is considered an ideal time to reassess the patient. Generally, the patient has been in our care for at least a year, and we now know him or her better. We should have another discussion about the goals of treatment. Have the goals changed as the patient has had time to process the diagnosis? How has his or her lifestyle changed? We reassess the patient's performance status according to criteria from the Eastern Cooperative Oncology Group (ECOG), and take stock of the patient's current quality of life. Other questions include: What is the current tumor burden? What has he or she given up because of the cancer? What toxicities have had the largest impact, and can they be managed better? What aspects of the prior treatments have been most and least bothersome? Points raised in this discussion can help guide the patient through the later half of the journey with mCRC, into the third-line setting and beyond.

There are now many choices for the treatment of mCRC after the initial exposure to fluorouracil-based chemotherapy in the first- and second-line settings. It is important to establish the biomarker and molecular profile of the patient's tumor, including the status of *RAS*, *BRAF*, *NTRK*, microsatellite instability, and HER2. Additionally, recent approvals now mean that a deeper molecular profile is necessary. For example, patients with a high level of microsatellite instability or mismatch repair–deficient mCRC qualify for treatment with pembrolizumab, an immunotherapy that targets the programmed death 1 receptor.[12] Patients should also be tested for the presence of *NTRK* fusions. This molecular abnormality was rarely tested for even just 1 year ago. Very few patients (an estimated <1%) with mCRC harbor this molecular alteration, but it can now be effectively targeted with the NTRK inhibitor larotrectinib, which is associated with robust tumor responses in *NTRK* fusion–positive cancers.[13] Without testing for this molecular alteration, appropriate patients will not receive this treatment.

In my practice, I review the patient's molecular testing to ensure that he or she has the most currently available data. When appropriate, I rebiopsy the tumor. In mCRC, the technology supporting molecular profiling, and the information provided, has greatly changed, even from just 2 years ago. Therefore, even if a patient undergoes molecular testing after the initial diagnosis, it is important to consider whether retesting might be beneficial.

Options for Third-Line Therapy

In the third-line setting, after a patient has received fluorouracil-based chemotherapy regimens with oxaliplatin, irinotecan, and, when indicated, EGFR-targeted agents, there are 2 primary choices that are approved by the US

Food and Drug Administration (FDA): regorafenib and trifluridine/tipiracil.[14,15] Both of these agents are administered orally. They can prolong survival (both overall survival and progression-free survival [PFS]) in heavily pretreated patients.[16,17] Notably, both drugs showed very little tumor regression in clinical trials, as evidenced by a very low overall response rate (ORR). Instead, they seem to stabilize cancer growth, as demonstrated by a consistent rate of stable disease.

An important concept regarding the incorporation of these drugs into the management course is to initiate them before patients become too frail and begin to experience a rapid fall in performance status. Clinical evidence now suggests that these drugs do not work as well in patients with a poor performance status, and therefore physicians should not wait too long (eg, by recycling chemotherapies) before initiating them. Recycling of chemotherapy agents has less support as a strategy to improve overall survival, and therefore should be saved for true salvage therapy.

Another treatment option that is perhaps less common, but still very effective, is local therapy. For example, in patients with liver-dominant disease, we will often consider a local therapeutic approach, such as yttrium-90 radioembolization or even selective radiation therapy in those with symptomatic recurrences. Notably, these localized treatments are considered even when the patient has extrahepatic disease, if the liver disease is the most life-threatening feature.

In many situations, these patients may be eligible for clinical trials. As we all know, early-phase studies have the potential to offer benefit, as evolution of clinical research moves toward nonrandomized trials, particularly those that incorporate precision medicine. Although checkpoint inhibitor immunotherapies have not superseded the chemotherapy foundation of mCRC treatment, as they have in other solid tumors, we are hoping that novel combinations incorporating these immunotherapies will prove beneficial.

With the myriad therapies now available for refractory mCRC, there is no single standard treatment pathway. Instead, variables such as patient-related factors, disease burden, and molecular profiling must be incorporated to create a tailored strategy.

Disclosure

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References

1. Key Statistics for Colorectal Cancer, 2019. American Cancer Society. https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html. Updated January 24, 2019. Accessed February 12, 2019.
2. Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed January 12, 2019.
3. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-1417.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer. Version 4.2018. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated October 19, 2019. Accessed January 24, 2019.
5. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med*. 2013;369(11):1023-1034.
6. Jaka A, Gutiérrez-Rivera A, López-Pestaña A, et al. Predictors of tumor response to cetuximab and panitumumab in 116 patients and a review of approaches to managing skin toxicity. *Actas Dermosifiliogr*. 2015;106(6):483-492.
7. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-345.
8. Saltz LB, Lenz HJ, Kindler HL, et al. Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. *J Clin Oncol*. 2007;25(29):4557-4561.
9. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705.
10. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15(6):569-579.
11. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357(20):2040-2048.
12. Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 2019.
13. Vitrakvi [package insert]. Stamford, CT: Loxo Oncology, Inc; 2018.
14. Stivarga [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2018.
15. Lonsurf [package insert]. Princeton, NJ: Taiho Oncology; 2017.
16. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
17. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.

Clinical Trial Data for Third-Line Therapy in Metastatic Colorectal Cancer

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It is always important to consider the goals of treatment for mCRC across all lines of therapy. In later lines of therapy, overall survival remains a critical outcome and thus is often the primary endpoint of clinical trials. Other measures of efficacy are also relevant, including PFS. Clinical trial data suggest that the magnitude of benefit in these measures of efficacy in the third-line setting are comparable with other therapies in earlier (second-line) settings. Therefore, when considering the continuum of care, it is important to ensure that patients are exposed to all available active therapies to maximize their survival.

Coupled with the goal of prolonging survival is the understanding that improving and maintaining quality of life remains a fundamental aspect of therapy. Treatment of patients with metastatic disease is primarily palliative. Although the therapies used in this setting provide the added bonus of prolonged survival, it is important to remember that quality of life should not be sacrificed. This is particularly important to consider in the later-line settings for mCRC, when heavily pretreated patients are more likely to be frail and fatigued at baseline.

There are currently 2 FDA-approved options for the treatment of mCRC in the third-line setting and beyond: regorafenib and the combined agent trifluridine/tipiracil.[1,2] Both agents have demonstrated benefit in patients with refractory mCRC and are included in the guidelines from the National Comprehensive Cancer Network (NCCN).[3]

Clinical Trials of Regorafenib

Regorafenib is an orally available, small-molecule multikinase inhibitor that blocks the actions of several membrane-bound and intracellular kinases involved in oncogenesis, tumor angiogenesis, metastasis, and tumor immunity. At physiologically relevant concentrations, regorafenib or its major human active metabolites have been shown to inhibit the activity of RET, the VEGF receptors 1 to 3, the platelet-derived growth factor receptors α and β, and the fibroblast growth factor receptors 1 and 2, among others. In animal models, as well as some models for human CRC, regorafenib demonstrated antiangiogenic activity and inhibition of tumor growth and metastasis.[1]

The CORRECT Study

An initial phase 1b trial of patients with advanced CRC treated with regorafenib demonstrated preliminary evidence of antitumor activity, even in a heavily pretreated population. (Patients had received a median of 4 lines of prior therapy for metastatic disease.) In this group of 38 patients, the disease control rate was 74%.[4] Based on these promising results, the phase 3 CORRECT trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was designed to more fully characterize the efficacy and safety of regorafenib in this setting.[5] CORRECT was a randomized, double-blind, placebo-controlled phase 3 international study performed across multiple sites throughout North America, Europe, Asia, and Australia. A total of 760 patients with mCRC were randomly assigned in a 2:1 fashion to treatment with either regorafenib (160 mg once daily) or placebo, administered for the first 3 weeks of 4-week cycles. Patients in both arms also received best supportive care. Treatment was continued until disease progression or unacceptable toxicity. Randomization was stratified according to prior treatment with VEGF-targeted agents, time from diagnosis of metastatic disease, and geographic region. No crossover between treatment arms was allowed.[5]

The CORRECT trial enrolled patients who had developed disease progression during administration of the last standard therapy or within 3 months after treatment, as well as patients who had experienced an intolerable treatment-related toxicity.[5] Acceptable standard therapies varied widely in this international trial. However,

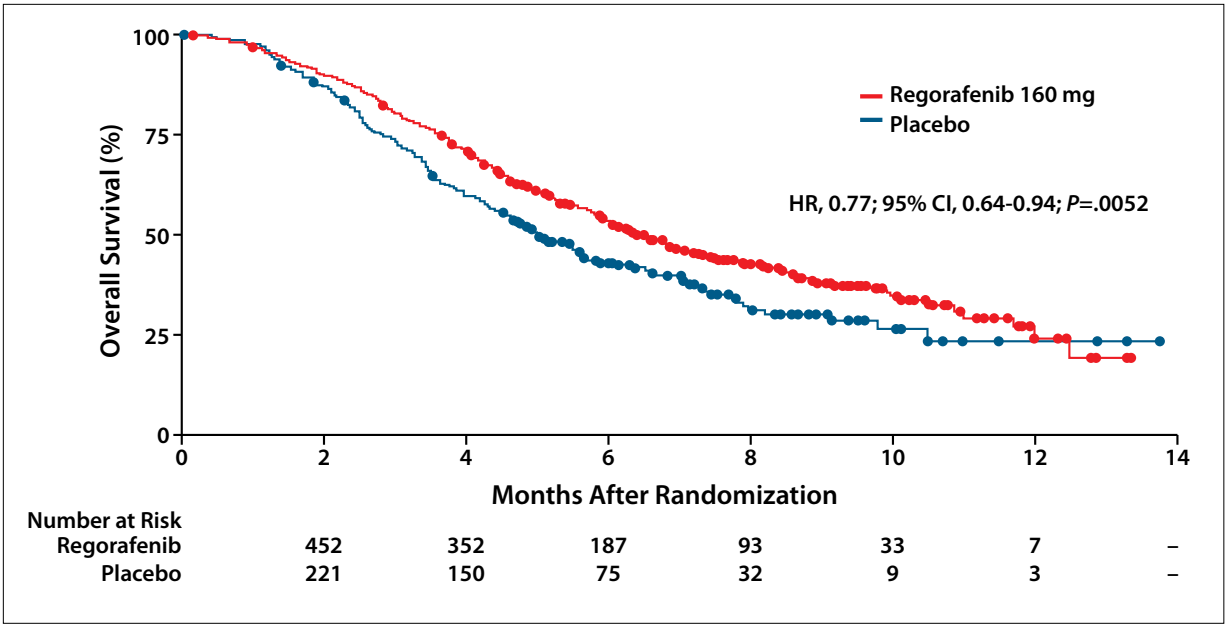

Figure 2. Median overall survival in the phase 3 CORRECT trial, which compared regorafenib vs placebo. CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. *Lancet*. 2013;381(9863):303-312.[5]

previous treatment had to include as many of the following agents as were approved in the patient's geographic location: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab; as well as cetuximab or panitumumab for patients with *KRAS* wild-type tumors.

Overall, baseline characteristics were similar between the treatment arms. An exception was the frequency of the *KRAS* mutation, which was 54% in the regorafenib arm and 62% in the placebo arm. The median age in both arms was 61 years, 61% of the population was male, and 78% were white. Most patients (83%) were recruited from North America, Western Europe, Israel, and Australia. Patients had an ECOG performance status of either 0 (54%) or 1 (46%). The colon was the primary site of disease (65%), with adenocarcinoma accounting for most tumor histologies (97%). Patients in this trial were heavily pretreated; 48% had received 4 or more prior systemic treatments for their metastatic disease. All patients in both arms had received prior treatment with bevacizumab. Among patients in the regorafenib arm, 83% were most recently treated with fluoropyrimidine, 80% with bevacizumab, 80% with irinotecan, 55% with oxaliplatin, and 43% with panitumumab, cetuximab, or both. (For the placebo arm, these rates were 87%, 84%, 90%, 63%, and 42%, respectively.)

The primary endpoint of the CORRECT study was overall survival. At the second planned interim analysis, the median overall survival was 6.4 months in the regorafenib arm vs 5.0 months in the placebo arm (hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; *P*=.0052; Figure 2).[5] This result crossed the prespecified overall survival efficacy boundary, and was considered statistically significant. At 6 months, the estimated rate of overall survival was 52.5% with regorafenib vs 43.5% with placebo. The 12-month estimated overall survival rates were 24.3% vs 24.0%, respectively. The survival benefit with regorafenib was evident across all patient subgroups, with the exception of patients with rectal cancer (although this subgroup was small).

Secondary efficacy endpoints included PFS, ORR, and disease control rate. Median PFS was 1.9 months with regorafenib vs 1.7 months with placebo (HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001).[5] The ORR was 1.0% with regorafenib and 0.4% with placebo (*P*=.19); all responses were partial. The disease control rate, which included patients who achieved stable disease as well as a response, was significantly higher in the regorafenib arm, at 41%, vs 15% in the placebo arm (*P*<.0001). Among patients who achieved stable disease, the median duration was 2.0 months with regorafenib and 1.7 months with placebo.

In the CORRECT study, treatment-related adverse events occurred at a greater frequency among patients who received regorafenib vs placebo (93% vs 61%).[5] Grade 3 or higher treatment-related adverse events were reported in 54% of regorafenib-treated patients and 14% of placebo-treated patients. The most frequent grade 3 or higher treatment-related adverse events reported with regorafenib were hand-foot skin reaction (17%), fatigue

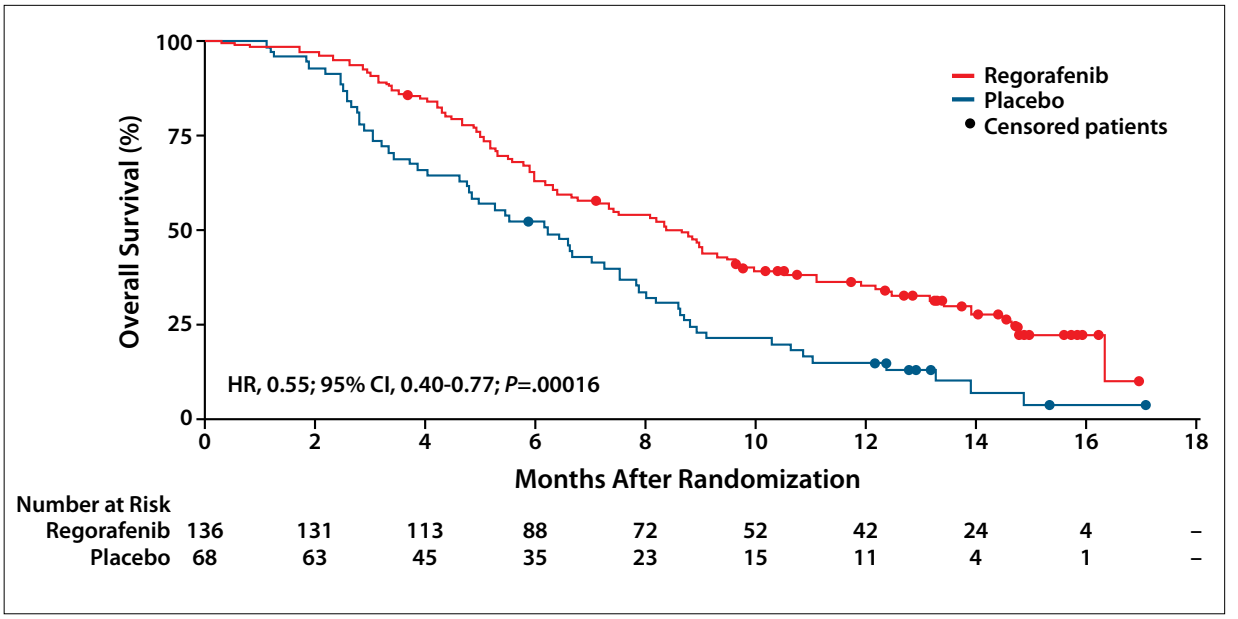

Figure 3. In the phase 3 CONCUR trial, median overall survival was improved with regorafenib vs placebo. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.[6]

(10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%).

The CONCUR Study

Among the 760 patients randomly assigned to treatment in the CORRECT study, only 15% were Asian (mostly Japanese).[5] The similarly designed CONCUR trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was conducted to demonstrate the efficacy and safety of regorafenib in the heavily pretreated setting among a larger and more representative population of Asian patients with mCRC.[6] These patients were less likely to have received previous treatment with biologic agents.

CONCUR was a randomized, double-blind, placebo-controlled, parallel-group phase 3 study conducted across several Asian countries, including China, Hong Kong, South Korea, Taiwan, and Vietnam.[6] The study enrolled 204 patients with mCRC who were randomly assigned in a 2:1 fashion to treatment with regorafenib at 160 mg once daily or placebo, given for the first 3 weeks of each 4-week cycle. Patients in both treatment arms also received best supportive care. Treatment was continued until disease progression or unacceptable toxicity. At the time of randomization, patients were stratified by the number of metastatic sites and the time from diagnosis of metastatic disease.

Eligible patients had measurable or nonmeasurable mCRC. They had received at least 2 prior lines of therapy, which included a fluoropyrimidine plus oxaliplatin or irinotecan. Previous treatment with bevacizumab, cetuximab, or panitumumab was also permitted. Patients had developed progressive disease by 3 months after the last standard treatment (or within 6 months of stopping adjuvant oxaliplatin), or they stopped standard treatment after experiencing intolerable toxicity.[6]

Baseline characteristics were balanced across the 2 treatment arms. The median patient age was 57.5 years in the regorafenib arm and 55.5 years in the placebo arm. In the regorafenib arm, patients were older (≥65 years) and more likely to be male. Patients had an ECOG performance status of either 0 (25%) or 1 (75%). The colon was the main site of disease (62%), and most tumors were of adenocarcinoma histology (96%). Approximately 31% of patients had a *KRAS* mutation at baseline. Most patients had multiple sites of metastatic disease (79%), and 39% had received 4 or more prior systemic treatments for their metastatic disease.[6]

The primary endpoint of the CONCUR study, overall survival, was a median of 8.8 months with regorafenib vs 6.3 months with placebo (HR, 0.55; 95% CI, 0.40-0.77; *P*=.00016; Figure 3).[6] The benefit in overall survival was consistent across all patient subgroups. In an exploratory analysis of overall survival according to prior targeted biologic therapy, the HR for survival was 0.31 (95% CI, 0.19-0.53) among patients who had not previously received targeted therapy and 0.78 (95% CI, 0.51-1.19) among patients who had received at least 1 prior targeted agent.

PFS, a secondary endpoint of CONCUR, was also significantly improved with regorafenib vs placebo. Median PFS was 3.2 months vs 1.7 months, respectively (HR, 0.31; 95% CI, 0.22-0.44; *P*<.0001).[6] The ORR, another secondary endpoint, was 4% with regorafenib (all partial responses). No responses were achieved in the placebo arm. The secondary endpoint of disease control rate was significantly higher with regorafenib vs placebo (51% vs 7%; *P*<.0001). Among patients who achieved stable disease, the median duration was 3.0 months with regorafenib vs 1.7 months with placebo.

The frequency of treatment-related grade 3 or higher adverse events was 54% with regorafenib vs 15% with placebo. In the regorafenib arm, the most frequent of these events were hand-foot skin reaction (16%), hypertension (11%), hyperbilirubinemia (7%), hypophosphatemia (7%), elevated alanine aminotransferase (ALT; 7%), elevated aspartate aminotransferase (AST; 6%), increased lipase (4%), and maculopapular rash (4%).[6]

The CONSIGN Study

The CONSIGN study (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy) assessed the safety profile of regorafenib in a larger, more-representative patient population.[7] The study also provided access to regorafenib prior to market authorization to patients with treatment-refractory mCRC. CONSIGN was a prospective, open-label, single-arm phase 3b study conducted throughout Europe, North America, Israel, and Australia. Patient eligibility was similar to that in the CORRECT study. Patients had received approved standard therapies, including a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab/panitumumab (for patients with *KRAS* wild-type tumors). All patients had developed disease progression within 3 months of completing their last treatment.

Among the 2872 patients enrolled, 2864 received treatment with regorafenib (160 mg once daily for the first 3 weeks of a 4-week cycle). The primary endpoint of the study was safety, and PFS was the only efficacy objective. The median patient age was 62 years, and most patients were male (59%) and white (83%). The colon was the primary site of disease in 64% of patients, and 77% of patients had liver metastases at baseline. Nearly all patients (96%) had received prior bevacizumab. A protocol amendment permitted enrollment of some patients from Mexico and Russia who had not received bevacizumab. Nearly half of patients (46%) had previously received 4 or more prior therapies for metastatic disease.[7]

Treatment-emergent adverse events required a dose reduction in 46% of patients. In 9% of patients, treatment was discontinued owing to regorafenib-related treatment-emergent adverse events. The most frequently reported grade 3 or higher treatment-emergent adverse events reported with regorafenib were hypertension (15%), hand-foot skin reaction (14%), fatigue (13%), diarrhea (5%), and hypophosphatemia (5%). Treatment-emergent grade 3 or 4 laboratory abnormalities included increased bilirubin (13%), increased AST (7%), and increased ALT (6%).[7]

Grade 3 or higher treatment-emergent adverse events that were considered to be related to regorafenib occurred in 55% of patients younger than 65 years, 59% of those ages 65 to 74 years, and 64% in those 75 years or older. In the oldest group of patients (those ages ≥75 years), rates of grade 3 or higher regorafenib-related fatigue and hypertension were higher than in their younger counterparts. Duration of treatment, median number of cycles, and daily dose did not differ markedly according to patient age.[7]

The median PFS in the overall CONSIGN population was 2.7 months (95% CI, 2.6-2.7), and was similar for patients with *KRAS* wild-type tumors (2.8 months; 95% CI, 2.7-2.9) and *KRAS* mutant tumors (2.5 months; 95% CI, 2.4-2.6). The estimated 6-month and 12-month PFS rates were 15% and 4%, respectively. Approximately one-quarter of patients (23%) achieved a PFS of longer than 4 months. Exploratory analyses suggested that these patients were more likely to have an 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.[7]

The CORRELATE Study

The CORRELATE study was a prospective, observational clinical study that examined the tolerability of regorafenib in a real-world population of patients with mCRC.[8] The study was conducted across Europe, Latin America, and Asia. Patients had previously treated metastatic disease, and their physician had selected treatment with regorafenib.

A total of 1037 patients were enrolled in the CORRELATE trial. The median patient age was 65 years, 61% were male, and 62% were white. The ECOG performance status of patients was 0 in 41%, 1 in 46%, and 2 through 4 in 6%. Just over half of patients had a *KRAS* mutation (56%). The predominant metastatic site at baseline was the liver (72%), followed by the lungs (57%), bones (11%), and gastrointestinal tract (6%). Most patients had received prior treatment with a VEGF-targeted agent (86%). The median number of prior therapies was 3 (interquartile range, 2-4), and 39% had received 4 or more prior systemic treatments for metastatic disease.[8]

The CORRELATE study assessed the dosing of regorafenib in this real-world patient population. Among the total population of 1037 patients, 57% initiated treatment at 160 mg, 30% at 120 mg, and 13%

at 80 mg or lower. Patient age and ECOG performance status were similar between patients who received 160 mg vs 120 mg. Dose reductions were more frequent in patients who initiated treatment with 160 mg compared with 120 mg, although the percentages of patients requiring a dose interruption, delay, or another modification were similar. Among patients in the regorafenib arm, 49% discontinued treatment owing to radiologic disease progression and 19% discontinued owing to regorafenib-related treatment-emergent adverse events.[9]

The primary objective was to assess safety. All-grade treatment-emergent adverse events considered related to regorafenib occurred in 80% of patients, and were most commonly fatigue (41%), hand-foot skin reaction (26%), diarrhea (19%), mucositis (15%), hypertension (14%), and anorexia (13%). Grade 3 or higher treatment-emergent adverse events that were related to regorafenib occurred in 36% of patients. The most common of these were fatigue (9%), hand-foot skin reaction (7%), and hypertension (6%).[8]

Secondary objectives of CORRELATE included assessment of the effectiveness of regorafenib (as measured by overall survival and PFS). Patients were assessed according to the treating physician's routine practice. The median overall survival was 7.6 months (95% CI, 7.1-8.2), and the estimated rate of 1-year overall survival was 33.8%. The median PFS was 2.8 months (95% CI, 2.6-2.8), and the estimated rate of 6-month PFS was 18%.[8]

The IMblaze370 Study

Interestingly, the 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) recently offered additional evidence of the efficacy of regorafenib in the chemorefractory mCRC setting.[10] The trial compared single-agent regorafenib with a combination of atezolizumab, an immunotherapy that targets programmed death ligand 1 (PD-L1), plus the MEK inhibitor cobimetinib. Findings from this study, presented at the 2018 World Congress on Gastrointestinal Cancer, demonstrated that the immunotherapy-based combination failed to improve survival compared with regorafenib.

A total of 363 patients with mCRC were enrolled in the IMblaze370 study and randomly assigned in a 2:1:1 ratio to atezolizumab plus cobimetinib, atezolizumab alone, or single-agent regorafenib. In the combination arm, atezolizumab was given at 840 mg every 2 weeks and cobimetinib was administered at 60 mg for 3 weeks out of a 4-week cycle. When administered as a monotherapy, atezolizumab was dosed at 1200 mg every 3 weeks. Regorafenib was administered at a dose of 160 mg once daily for 3 weeks of a 4-week cycle.[10]

Baseline characteristics were similar across the 3 treatment arms. The median patient age was 56 to 59 years, and the ECOG performance status was 1 for approximately half of the study population and 0 for the rest. Approximately one-quarter of patients had received at least 3 prior lines of treatment. PD-L1 expression was confirmed in 34% to 43% of patients.[10]

The primary endpoint of overall survival was not met in the IMblaze370 trial. The median overall survival achieved with atezolizumab plus cobimetinib was 8.9 months, similar to the 8.5 months reported in the regorafenib arm (HR, 1.00; 95% CI, 0.73-1.38; *P*=.9871). For patients treated with atezolizumab monotherapy, the median overall survival was 7.1 months (HR compared with regorafenib, 1.19; 95% CI, 0.83-1.71; *P*=.3360). The estimated 12-month rate of overall survival was 38.5% with atezolizumab plus cobimetinib, 36.6% with regorafenib, and 27.2% with atezolizumab alone.[10]

Additionally, there were no differences in PFS among the 3 treatment arms.[10] The HR for PFS with atezolizumab plus cobimetinib compared with regorafenib was 1.25 (95% CI, 0.94-1.65). The HR for PFS with atezolizumab monotherapy compared with regorafenib was 1.39 (95% CI, 1.00-1.94). No complete responses were reported. The ORR was 2.7% with atezolizumab plus cobimetinib, 2.2% with atezolizumab monotherapy, and 2.2% with regorafenib. Stable disease lasting at least 6 weeks was reported in 32.2% of the regorafenib arm, 23.5% in the atezolizumab plus cobimetinib arm, and 18.9% in the atezolizumab monotherapy arm. The disease control rate was 34.4% with regorafenib, 26.2% with atezolizumab plus cobimetinib, and 21.1% with atezolizumab monotherapy.

Grade 3/4 treatment-related adverse events occurred in 45% of patients in the combination arm, 10% of patients in the atezolizumab monotherapy arm, and 49% of patients in the regorafenib arm. Discontinuation owing to adverse events occurred in 21% of patients in the combination arm, compared with 4% with atezolizumab monotherapy and 9% with regorafenib. The most frequent all-grade adverse events from any cause included diarrhea (reported in 65% of the combination arm, 19% of the atezolizumab monotherapy arm, and 38% of the regorafenib arm), rash (reported in 46%, 9%, and 24%, respectively), and fatigue (reported in 36%, 26%, and 46%, respectively). Several adverse events were reported at a higher frequency with regorafenib, including hypertension, weight decrease, hand-foot skin reaction, and dysphonia.[10]

The ReDOS Study

Regorafenib is associated with toxicities, such as hand-foot skin reaction and fatigue, that may impact use. In the CORRECT study, patients treated with regorafenib

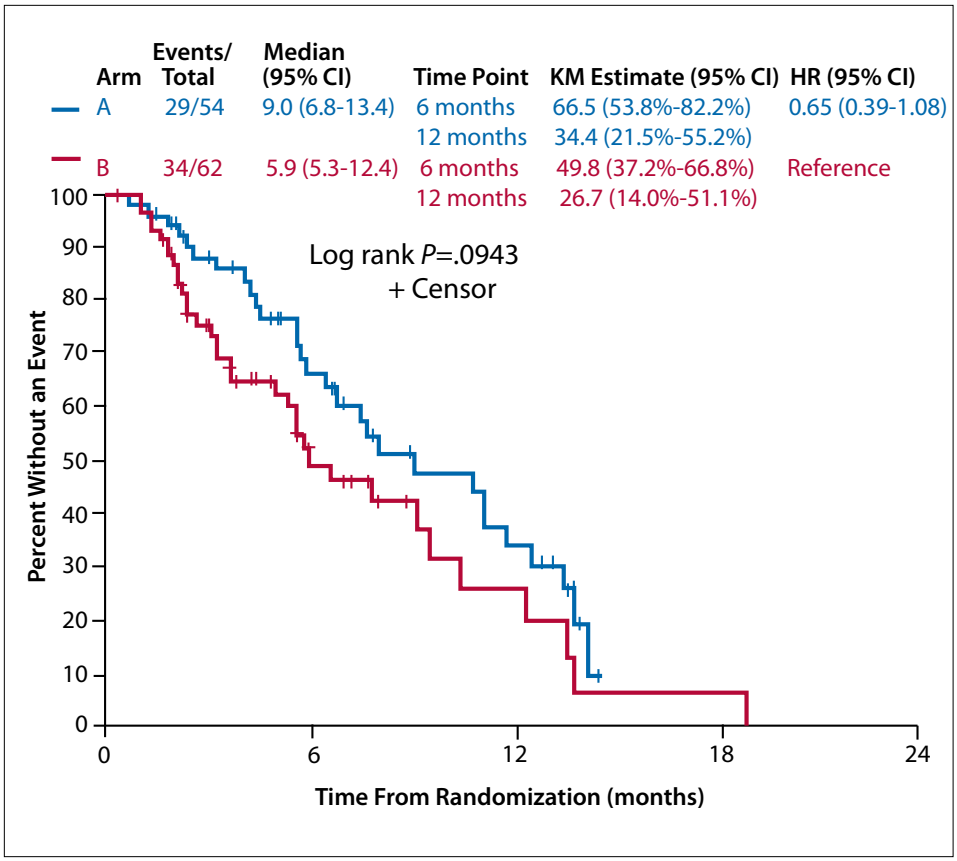

Figure 4. Overall survival in the randomized phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen. Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in the absence of significant drug-related toxicities. In arm B, patients received the standard dose of regorafenib at 160 mg/day. HR, hazard ratio; KM, Kaplan-Meier; ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab T et al. ASCO GI abstract 611. *J Clin Oncol.* 2018;36(suppl 4S).[11]

received 78.9% of the planned dose during the course of the study, compared with 90.1% for the placebo group.[5] Dose modifications were required in 76% of patients assigned to regorafenib (20% required ≥1 dose reduction and 70% required ≥1 dose interruption). The most common cause of dose modifications was adverse events.

The randomized phase 2 ReDOS trial (Regorafenib Dose Optimization Study) was conducted to evaluate a lower starting dose of regorafenib in patients with refractory mCRC.[11] The trial was designed with a planned dose escalation of regorafenib. The lower dosing strategy was compared with the standard dose. Patients were randomly assigned to regorafenib initiated at 2 different regimens. In the low-dose arm, patients began treatment with 80 mg once daily on days 1 to 7. This dose was escalated first to 120 mg once daily on days 8 to 14, then to 160 mg once daily on days 15 to 21, and then continued at 160 mg once daily every 3 weeks out of each subsequent 4-week treatment cycle. The standard-dose arm consisted of the approved dose of 160 mg once daily. Within each treatment group, patients were randomly assigned to either a preemptive or a reactive strategy for the management of hand-foot skin reaction. All patients enrolled in the ReDOS trial had received prior treatment with all of the standard regimens, including the appropriate biologic therapy.[11]

At baseline, the patients' median age was 61 years, and 61.2% were male. Patients had an ECOG performance status of either 0 (37.1%) or 1 (62.9%). Most patients had 3 or more metastatic sites (67.2%), and 46.6% of patients had *KRAS*-mutated disease.[11]

The study met its primary endpoint: the number of patients finishing cycle 2 at 8 weeks. This endpoint was met by 43% of patients in the escalating-dose arm vs 24% of patients in the standard-dose arm (P=.0281).[11] Secondary endpoints included overall survival, PFS, time to progression, cumulative doses, quality of life, and safety. The median overall survival was numerically higher in the escalating-dose arm, at 9.0 months, compared with 5.9 months in the standard-dose arm (HR, 0.65; 95% CI, 0.39-1.08; P=.0943; Figure 4). In the escalating-dose arm, the estimated overall survival rates were 66.5% at 6 months and 34.4% at 12 months. In the standard-dose arm, these rates were 49.8% and 26.7%, respectively. The median PFS was 2.5 months in the escalating-dose arm vs 2.0 months in the standard-dose arm (HR, 0.89; 95% CI, 0.59-1.33; P=.5534; Figure 5). In the escalating-dose arm, the estimated PFS rates were 12.2% at 6 months and 2.4% at 12 months. These rates were 11.8% and 5.9%, respectively, in the standard-dose arm.

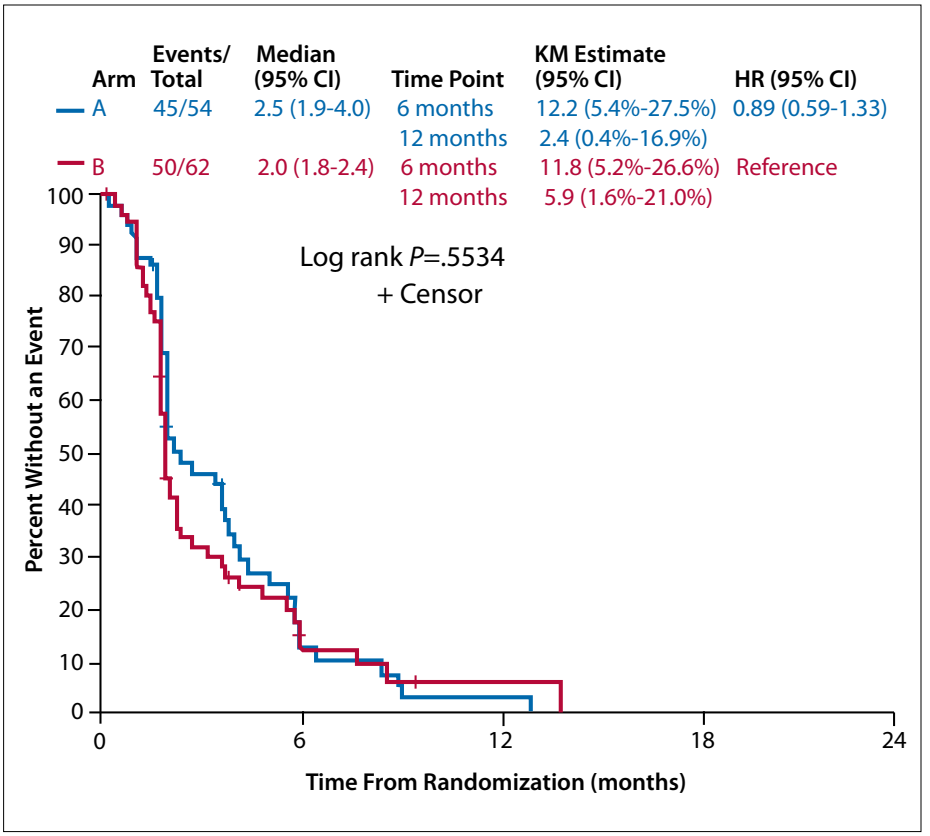

Figure 5. Progression-free survival in the randomized phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen. Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in the absence of significant drug-related toxicities. In arm B, patients received the standard dose of regorafenib at 160 mg/day. HR, hazard ratio; KM, Kaplan-Meier; ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab T et al. ASCO GI abstract 611. *J Clin Oncol*. 2018;36 (suppl 4S).[11]

At 2 weeks from the initiation of therapy, the dose-escalation strategy did not appear to compromise quality of life, unlike the standard-dose administration. Additionally, rates of grade 3/4 fatigue were lower in the escalating-dose arm vs the standard-dose arm (13.0% vs 17.7%, respectively), as were rates of grade 3/4 hypertension (7.4% vs 14.5%) and grade 3/4 maculopapular rash (0% vs 4.8%).[11]

Overall Conclusions for the Regorafenib Clinical Trial Data

Following the efficacy demonstrated in the CORRECT study, regorafenib received FDA approval for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy.[1] The CONCUR trial demonstrated a similar benefit in an Asian population.[6] Interestingly, the magnitude of the benefit in overall survival and PFS between the regorafenib and placebo arms was historically larger in the CONCUR study compared with the CORRECT study. This difference might be attributed to the slightly earlier use of regorafenib in a less pretreated population (40% of patients had not received treatment with a prior biologic therapy).

The efficacy and safety of regorafenib in the third-line setting or later were further established in 2 observational studies conducted in real-world populations: CONSIGN and CORRELATE.[7,8] Importantly, in these studies, the improvements in overall survival and PFS with regorafenib were similar to those observed in the CORRECT and CONCUR trials. These real-world observational trials also demonstrated another key point regarding regorafenib treatment: there is a great deal of dosing and schedule variability, primarily owing to the treatment-emergent adverse events.

The idea of alternative dosing for regorafenib was further examined in the ReDOS study.[11] The results of this study suggested that an initial strategy of regorafenib dose escalation improved the likelihood that patients would tolerate the first 2 cycles of treatment, meaning they were more likely to be able to start cycle 3. This dosing strategy is now included as an option in the NCCN treatment guidelines.[3]

Clinical Trials of Trifluridine/Tipiracil

Trifluridine/tipiracil is an orally available agent that combines the thymidine-based nucleic acid analogue trifluridine with the thymidine phosphorylase inhibitor tipiracil

hydrochloride. Trifluridine is the active cytotoxic component, which kills cells through its incorporation into DNA, and tipiracil hydrochloride works to prevent the rapid degradation of the trifluridine and maintain steady-state levels of the drug.[12,13]

The RECOURSE Study

After initial phase 1 and 2 clinical trials demonstrated that trifluridine/tipiracil was active in patients with mCRC who were refractory to treatment, the RECOURSE study (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) was conducted to more fully assess this agent's safety and efficacy in a broader patient population.[14] RECOURSE was a double-blind, randomized phase 3 study that enrolled 800 patients with refractory mCRC. Patients had received at least 2 prior standard treatments (which could have included adjuvant chemotherapy), and had experienced either disease progression within 3 months after the last administration of chemotherapy or had developed intolerable toxicity with that therapy. Patients had received chemotherapy with each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, as well as cetuximab or panitumumab (for patients who have *KRAS* wild-type tumors).

Patients were randomly assigned in a 2:1 fashion to 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. Treatment cycles were repeated up to 4 times. Both treatment arms additionally received best supportive care. Patients were stratified by *KRAS* status, the time from first diagnosis of metastasis, and geographic region. Patients were enrolled in the United States, Europe, Australia, and Japan. Baseline demographics and disease characteristics were well-balanced between the 2 treatment arms. Patients had a median age of 63 years, 61% were male, and 58% were white. Just over half (56%) had an ECOG performance status of 0, and the remaining 44% had an ECOG performance status of 1. The primary site of disease was the colon in 62% of patients. Most patients (61%) had received 4 or more prior therapies.[14]

The primary endpoint, overall survival, was reached. 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; Figure 6).[14] The survival benefit with trifluridine/tipiracil was observed across nearly all prespecified patient subgroups. The estimated rates of 1-year overall survival were 27% with trifluridine/tipiracil vs 18% with placebo.

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). This benefit was observed across all patient subgroups. Among the patients evaluable for tumor response, 8 patients in the trifluridine/tipiracil arm had a partial response, and 1 patient in the placebo arm had a complete response (ORR of 1.6% vs 0.4%; *P*=.29). The disease control rate was significantly higher in the trifluridine/tipiracil arm vs the placebo arm (44% vs 16%, respectively; *P*<.001).[14]

Treatment with trifluridine/tipiracil compared with placebo resulted in a significant delay in the worsening of ECOG performance status from baseline levels of 0 or 1 to 2 or higher. The median time to an ECOG performance status of 2 or higher was 5.7 months with trifluridine/tipiracil vs 4.0 months with placebo (HR, 0.66; 95% CI, 0.56-0.78; *P*<.001).[14]

In the RECOURSE study, adverse events of grade 3 or higher were more frequent with trifluridine/tipiracil vs placebo. They included neutropenia (38% vs 0%), anemia (18% vs 3%), and thrombocytopenia (5% vs <1%). Patients in the trifluridine/tipiracil arm were also more likely than those in the placebo arm to develop grade 3 or higher nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%).[14]

The TERRA Study

The randomized, double-blind, placebo-controlled phase 3 TERRA trial (Study of TAS-102 in Patients With Metastatic Colorectal Cancer in Asia) evaluated trifluridine/tipiracil in Asian patients with mCRC.[15] The study drew patients from 30 sites in China, the Republic of Korea, and Thailand. The study randomly assigned patients in a 2:1 ratio to treatment with trifluridine/tipiracil (n=271) or placebo (n=135). The risk of death was significantly lower with trifluridine/tipiracil vs placebo (HR for death, 0.79; 95% CI, 0.62-0.99; log-rank *P*=.035). The median overall survival was 7.8 months with trifluridine/tipiracil vs 7.1 months with placebo. The incidence of serious adverse events was similar in both arms.

Overall Conclusions for the Trifluridine/Tipiracil Clinical Trial Data

Results from the RECOURSE study led to the FDA approval of trifluridine/tipiracil for patients with mCRC who had been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF biologic therapy; and, if *RAS* wild-type, an anti-EGFR therapy.[2] The efficacy outcomes, including the duration of overall survival and PFS, as well as tumor response rates, were similar between trifluridine/tipiracil in the RECOURSE study and regorafenib in the CORRECT study. However, data from clinical studies cannot be compared, and these 2 agents have not been evaluated in a head-to-head trial.

The confirmatory TERRA study reported similar efficacy with trifluridine/tipiracil in an Asian population

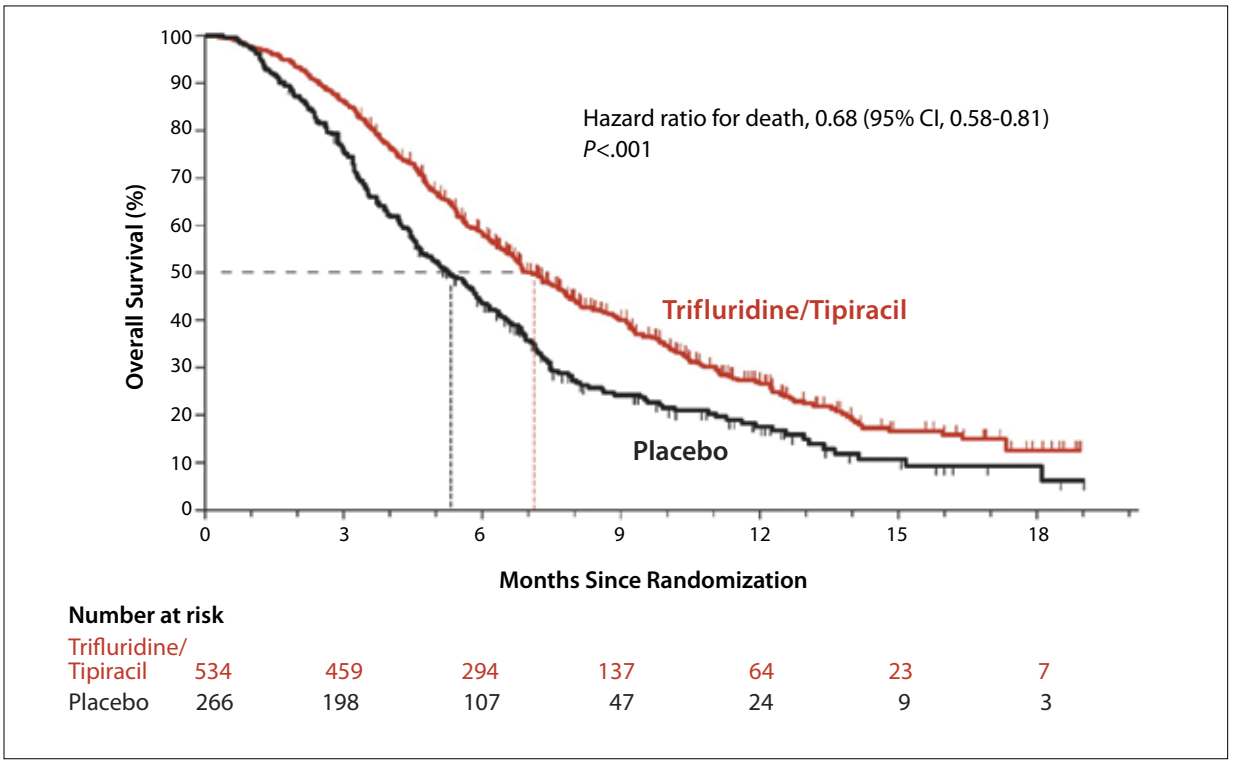

Figure 6. Overall survival in the phase 3 RECOURSE trial, which compared trifluridine/tipiracil vs placebo. RECOURSE, Randomized, Double-Blind, Phase 3 Study of TAS-102 Plus Best Supportive Care [BSC] Versus Placebo Plus BSC in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies. Adapted from Mayer RJ et al. *N Engl J Med*. 2015;372(20):1909-1919.[14]

that had an overall lower exposure to biologic agents.[15] Unlike the data for regorafenib in CONCUR vs CORRECT,[5,6] the magnitude of survival benefit reported in the TERRA study was historically similar to that reported in the RECOURSE trial.[14]

Disclosure

Dr Bekaii-Saab is a consultant for AbbVie, Armo, SillaJen, Imugene, and Immuneering.

References

1. Stivarga [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; 2018.
2. Lonsurf [package insert]. Princeton, NJ: Taiho Oncology, Inc; 2017.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer. Version 4.2018. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated October 19, 2019. Accessed January 24, 2019.
4. Strumberg D, Scheulen ME, Schultheis B, et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. *Br J Cancer*. 2012;106(11):1722-1727.
5. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
6. Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.
7. Van Cutsem E, Martinelli E, Cascinu S, et al. Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: results of the large, single-arm, open-label phase IIIb CONSIGN study. *Oncologist*. 2019;24(2):185-192.
8. Ducreux M, Petersen LN, Öhler L, et al. Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice: final analysis from the prospective, observational CORRELATE study [ESMO GI abstract O-012]. *Ann Oncol*. 2018;29(suppl 5).
9. O'Connor JM, Ducreux M, Petersen LN, et al. Real-world dosing of regorafenib (REG) in metastatic colorectal cancer (mCRC): final results from the prospective, observational CORRELATE study [ESMO abstract 463P]. *Ann Oncol*. 2018;29(suppl 8).
10. Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer [ESMO GI abstract LBA-004]. *Ann Oncol*. 2018;29(suppl 5).
11. Bekaii-Saab TS, Ou FS, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): a phase II randomized study of lower dose regorafenib compared to standard dose regorafenib in patients with refractory metastatic colorectal cancer (mCRC) [ASCO abstract 611]. *J Clin Oncol*. 2018;36(suppl 4S).
12. Tanaka N, Sakamoto K, Okabe H, et al. Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. *Oncol Rep*. 2014;32(6):2319-2326.
13. Fukushima M, Suzuki N, Emura T, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2′-deoxyribonucleosides. *Biochem Pharmacol*. 2000;59(10):1227-1236.
14. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.
15. Xu J, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study. *J Clin Oncol*. 2018;36(4):350-358.

Management of Patients With Relapsed/ Refractory Metastatic Colorectal Cancer

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By the time patients with mCRC reach the third-line setting, there is an established history of their treatments and the side effects that arose. In addition, the physician typically has a clear understanding of the patient's treatment goals. Several treatment options are available for refractory mCRC. Patients can be rechallenged with prior lines of therapy, particularly when they tolerated these agents well. Additionally, 2 agents—regorafenib and trifluridine/tipiracil—have proven effective in multiple clinical trials, prolonging both overall survival and PFS. Furthermore, clinical trials of novel agents and combinations can be considered in this setting. Selection among these treatment options depends on the preferences of both the physician and the patient, and will reflect the patient's experiences as well as the evolving goals of therapy.

Sequencing Regorafenib and Trifluridine/ Tipiracil

In clinical practice, patients generally benefit from being treated with all active agents. For third-line mCRC, regorafenib and trifluridine/tipiracil are both effective options. Therefore, it is important to create strategies that do not exclude the use of either agent, but instead allow both agents to be administered sequentially.

Clinical studies have shown that the efficacy of regorafenib is most apparent in patients with a good performance status (ie, an ECOG performance status of 0 or 1). For example, in the CONSIGN study, 23% of patients achieved a PFS exceeding 4 months.[1] An exploratory analysis found that these patients were more likely to have an ECOG performance status of 0, no liver metastases, and a longer time since diagnosis of metastatic disease as compared with patients who had a PFS of less than 4 months. Clinical data suggest that for patients with an ECOG performance status of 2 or higher, regorafenib is less likely to prolong survival. In addition, the toxicity profile associated with regorafenib would also preclude the use of this agent in already frail, less-fit patients with a deteriorated performance status.

For these reasons, in patients with a good performance status, I generally treat with regorafenib before trifluridine/tipiracil. Importantly, clinical data support the efficacy of trifluridine/tipiracil when given after regorafenib. For example, 18% of the population of the RECOURSE study had received prior regorafenib in addition to other systemic therapies.[2] Overall survival was similar regardless of whether patients had received prior treatment with regorafenib (HR, 0.69; 95% CI, 0.45-1.05) or had not (HR, 0.69; 95% CI, 0.57-0.83).

For patients with good or borderline performance status, I would hesitate to administer trifluridine/tipiracil first, as their performance status might deteriorate when treated with this cytotoxic drug. This might potentially prevent a patient from receiving regorafenib. This consideration is also applicable to additional lines of systemic therapy. In general, clinicians should not recycle through too many additional lines of cytotoxic treatment before initiating regorafenib.

When formulating a sequencing strategy for later lines of therapy in patients with mCRC, access to clinical trials should not be overlooked. Many novel agents and combinations are in active clinical development for mCRC. Unfortunately, some of these strategies have not improved outcomes. For example, early signs of activity with the combination of atezolizumab plus cobimetinib did not translate into prolonged survival over the current standard of care, regorafenib, in the IMblaze370 study.[3] However, these failures should not prevent physicians from considering appropriate patients for rationally designed clinical trials, which are available across the country. Many ongoing studies are evaluating treatments in the third-line setting, at the point when patients are being considered for regorafenib or trifluridine/tipiracil. This means that there is a certain window of opportunity for these patients to enter into clinical trials.

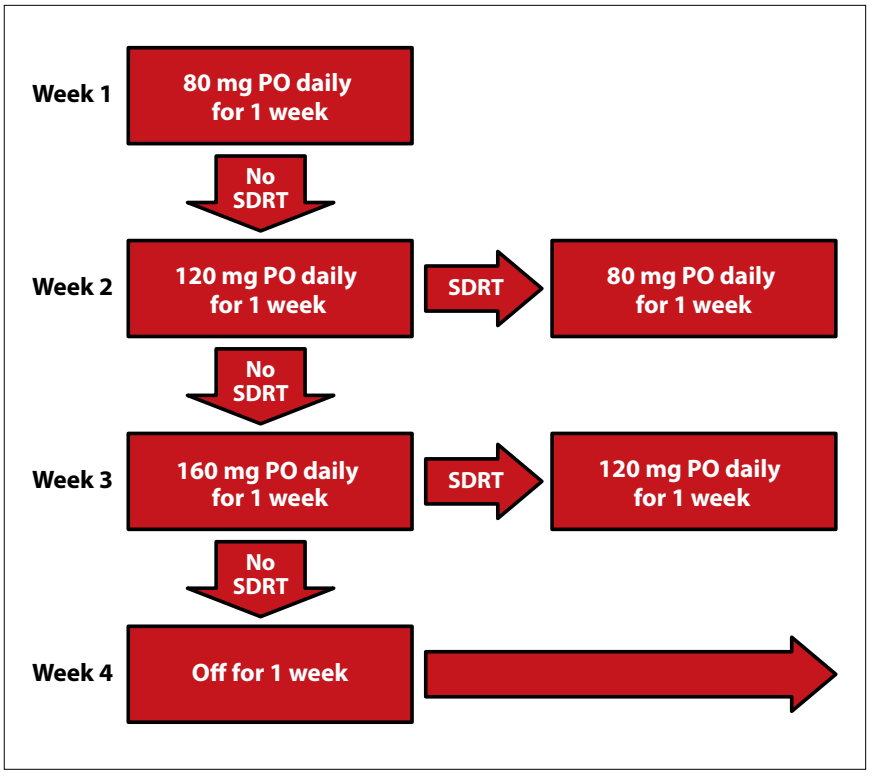

Figure 7. An incremental dose-escalation protocol for regorafenib can minimize toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol*. 2015;13(8):514-517.[5]

Clinical Use of Regorafenib

Given that regorafenib is a cytostatic agent, the best magnitude of benefit occurs with prolonged administration. Therefore, strategies aim to permit the patient to continue treatment for as long as possible. The dose-escalation strategy for regorafenib, evaluated in the ReDOS trial, is now becoming the standard of care in clinical practice.[4] This strategy involves the initial dose of 80 mg daily for the first week of treatment, then 120 mg daily for the second week of treatment, then escalating to the final dose of 160 mg daily for the third week of treatment (Figure 7).[5] This strategy is designed to lessen key toxicities associated with regorafenib, which typically occur within the first 1 to 2 weeks of exposure. Most notable of these side effects are hand-foot skin reaction and fatigue, which can significantly impact quality of life and require dose interruptions and discontinuations. In 2018, the NCCN guidelines were updated to include the ReDOS dosing strategy as a recommended option for the use of regorafenib in patients with relapsed/refractory mCRC.[6]

Even though regorafenib is an oral therapy, patients will still benefit from education regarding potential adverse events. In my clinical practice, when I initiate treatment with regorafenib, I first describe the potential side effects to the patient. I highlight fatigue and hand-foot skin reactions (Figure 8). When patients are aware of the possibility of these events, they are less frightened if they do occur. Patients require active management throughout the administration of regorafenib. In my practice, we typically see patients back in the clinic a week after they initiate regorafenib to assess any side effects. If the patient cannot come to the clinic, then we discuss any adverse events during a phone call.

Figure 8. Grade 3 hand-foot skin reaction. Reprinted from Frenette CT. *Clin Adv Hematol Oncology*. 2016;14(suppl 12):3-5.[8]

In my experience, hand-foot skin reaction is a common side effect of regorafenib, and it can be severe. It is

unknown whether the use of topical corticosteroids on hands and feet may prevent or mitigate the development of this inflammatory early reaction. We recommend that patients take reasonable precautions prior to starting regorafenib, including wearing comfortable shoes, removing calluses on the pressure zones of the feet, and moisturizing the feet using urea-based keratolytic lotions.

Clinical Use of Trifluridine/Tipiracil

Trifluridine/tipiracil tends to have a lower frequency of bothersome toxicities. The main side effect of trifluridine/tipiracil is neutropenia, but it is largely asymptomatic. There are few cases of febrile neutropenia. More than 50% of patients present with grade 3 or 4 neutropenia after their first cycle of trifluridine/tipiracil.[2] This side effect appears to correlate with better efficacy outcomes; patients with the most severe and early cases of neutropenia tend to have the best efficacy with trifluridine/tipiracil.[7] Therefore, the appropriate management for patients who experience even severe neutropenia typically includes delay of the onset of the second cycle by approximately a week. This strategy usually allows patients to tolerate the treatment and continue without developing febrile neutropenia over time.

Disclosure

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

References

1. Van Cutsem E, Martinelli E, Cascinu S, et al. Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: results of the large, single-arm, open-label phase IIIb CONSIGN study [published online September 6, 2018]. *Oncologist*. doi:10.1634/theoncologist.2018-0072.
2. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.
3. Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer [ESMO GI abstract LBA-004]. *Ann Oncol*. 2018;29(suppl 5).
4. Bekaii-Saab TS, Ou FS, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): randomized phase II trial to evaluate dosing strategies for regorafenib in refractory metastatic colorectal cancer (mCRC). An ACCRU Network study [ASCO GI abstract 611]. *J Clin Oncol*. 2018;36(4 suppl).
5. Grothey A. Regorafenib in metastatic colorectal cancer: optimal dosing and patient selection recommendations. *Clin Adv Hematol Oncol*. 2015;13(8):514-517.
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer. Version 4.2018. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Updated October 19, 2019. Accessed January 24, 2019.
7. Kasi PM, Kotani D, Cecchini M, et al. Chemotherapy induced neutropenia at 1-month mark is a predictor of overall survival in patients receiving TAS-102 for refractory metastatic colorectal cancer: a cohort study. *BMC Cancer*. 2016;16:467.
8. Frenette CT. Second-line therapy for patients with hepatocellular carcinoma. *Clin Adv Hematol Oncology*. 2016;14(suppl 12):3-5.

Sequencing Beyond the Second-Line Setting in Metastatic Colorectal Cancer: Further Observations

Axel Grothey, MD, John L. Marshall, MD, and Tanios Bekaii-Saab, MD

Axel Grothey, MD When would you choose to recycle chemotherapy vs start a new oral agent in the third-line setting?

John L. Marshall, MD The first consideration is to decide whether the chemotherapy is likely to work again. For example, if I have stopped oxaliplatin fairly early, after just 3 months, and the patient has had a good initial response to that treatment, then recycling oxaliplatin would likely help to further the response. The next consideration I make is whether the patient has a tumor burden that necessitates a response. For example, in patients with a symptomatic tumor burden, I would prioritize chemotherapy recycling, whereas in patients who develop asymptomatic progression and still have a good performance status, I would postpone recycling of chemotherapy until later. In these latter cases, I would opt for one of the newer oral targeted therapies, for which stable disease is a perfectly adequate endpoint.

Axel Grothey, MD How often do you use circulating tumor DNA for molecular profiling? I wonder about this question in the following context: when a cancer is

rebiopsied, are the results from a metastatic site representative of the whole cancer tumor load in the patient?

John L. Marshall, MD I have been involved with tissue-based analysis on a national level. I do not perform circulating DNA testing in mCRC.

Tanios Bekaii-Saab, MD The molecular profiling of mCRC via circulating free-tumor DNA is an exciting modality that could, in the future, complement or even replace tissue-based profiling. However, it is not yet ready to replace tumor-based profiling. I have used it in few cases. For example, I have used it when there was limited or no tissue, particularly when I suspected a *BRAF* mutation, which would change treatment. I have also used molecular profiling to monitor mutations and identify emerging mutations, especially with patients on targeted therapies, because this information could impact treatment decisions. In general, however, I have limited the use of molecular profiling to rare cases of when tissue is not available, as a complement to tissue biopsy, or as a follow-up to response or progression.

Axel Grothey, MD Some of the tissue-based molecular features that we are able to initially identify, such as *KRAS* mutation status and *BRAF* mutation status, are not likely to change. I test for circulating tumor DNA only to follow some emerging resistance mechanisms. For example, if a patient with *KRAS* wild-type cancer loses response to an EGFR-targeted therapy, it may be possible to identify some emerging *KRAS* or *BRAF* mutations in the circulating tumor DNA test.

John L. Marshall, MD It is important to note, however, that in mCRC, agents that target particular mutations are limited.

Axel Grothey, MD Would you use EGFR-targeted antibodies in the third-line setting for patients with right-sided, *KRAS*/*BRAF* wild-type mCRC?

John L. Marshall, MD I sometimes try this approach in patients who are still in adequate health. My experience, however, has been disheartening, as I rarely see any evidence of clinical benefit in this setting. In contrast, in patients with left-sided disease, it is as if the tumor melts away. So I try EGFR-targeted antibodies in appropriate patients with right-sided disease, but only in the refractory setting.

Tanios Bekaii-Saab, MD I agree with you on the use of EGFR-targeted antibodies. This strategy is supported by the REVERCE trial (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), which evaluated regorafenib followed by cetuximab vs the reverse (Figure 9).[1] The survival advantage did not appear to differ between patients with left-sided or right-sided disease. Regorafenib or even trifluridine/tipiracil would be preferable to use ahead of an EGFR inhibitor. That said, the EGFR inhibitor would still have a role in some patients. The best approach is not known because the few data available come from an older study of cetuximab vs best supportive care in refractory patients. When the analysis was done of left-sided vs right-sided disease, cetuximab did not improve PFS over best supportive care in patients with right-sided disease.[2] However, there was a survival advantage that was maintained with exposure to cetuximab. This suggests that it still would be an acceptable and reasonable option once you exhaust other therapies in patients with a *KRAS* wild-type, right-sided tumor.

Axel Grothey, MD I would like to clarify a couple of points regarding the ReDOS study.[3] It is important to highlight that this study tested a strategy that was not low-dose vs high-dose, but low-dose escalating to the maximum tolerated dose. How many patients were able to proceed from 80 mg to 160 mg as planned in the ReDOS study?

Tanios Bekaii-Saab, MD It is indeed important to emphasize that ReDOS evaluated a dose-escalation strategy and did not compare a low dose vs a high dose. In the ReDOS study, between 15% and 20% of the patients in the dose-escalation arm were able to reach and maintain the 160 mg dose.[3] Interestingly, even on the standard dose of 160 mg, a similar percentage of patients were able to maintain dosing. Some of the best and most durable responders were treated with 160 mg. This is an important point to emphasize: 160 mg remains the goal, if tolerable and feasible.

Axel Grothey, MD Is the dose-escalating regimen from ReDOS now the standard of care? Is that how you use regorafenib in your practice?

John L. Marshall, MD It is. The data are compelling enough. Initially, physicians struggled with the standard dosing. An unintended consequence from this dose-escalation strategy is that the prescribing of this medicine requires more time to preauthorize and clear doses. Our staff spends a lot of time with this. If we change the dose amount midcycle, for example, by escalating a week later, then we may have to redo the entire process. This is a problem that must be solved with our insurance partners and our pharmaceutical partners in order to better manage the process.

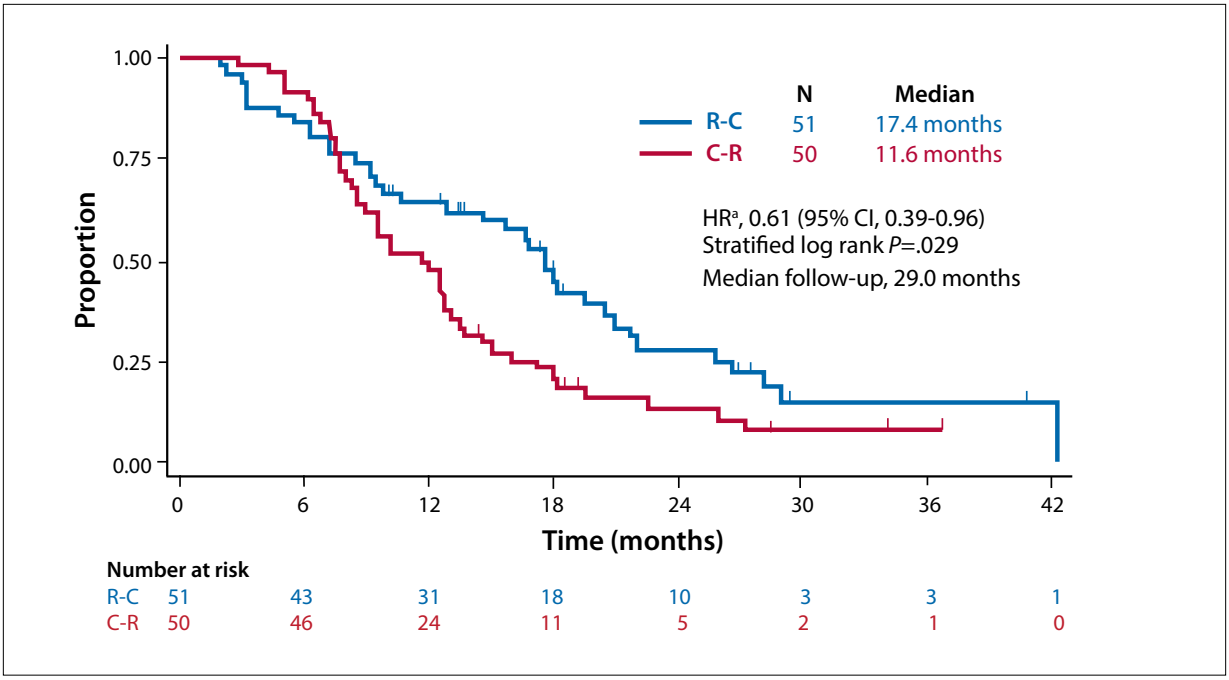

Figure 9. Median overall survival in the phase 2 REVERCE trial, which compared regorafenib followed by cetuximab (R-C) vs cetuximab followed by regorafenib (C-R) among patients with metastatic colorectal cancer. [a]Adjusted by intent to use irinotecan. HR, hazard ratio; REVERCE, Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus Reverse Sequence for Wild-Type *KRAS* Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan. Adapted from Tsuji Y et al. ASCO abstract 3510. *J Clin Oncol*. 2018;36(15 suppl).[1]

Axel Grothey, MD It is interesting that the more recent studies, such as IMblaze370 and ReDOS, showed better overall survival data than initial studies with regorafenib, such as CORRECT.[3-5] Why do you think that is?

Tanios Bekaii-Saab, MD There may be multiple factors. In the ReDOS trial, the dose-escalation strategy may have led to better survival. Another aspect is the ability to get patients to follow-up therapy. With the increased understanding of the need to educate both physicians and patients about the toxicities, we are now better able to help patients navigate into later lines of therapy.

The IMblaze370 study combined a PD-L1 immunotherapy and a MEK inhibitor.[3] This combination was associated with a high rate of toxicities. It became obvious to investigators that they needed to select more appropriate patients for study enrollment. In IMblaze370, the improved overall survival might partially relate to selection bias, meaning that patients were better able to tolerate the potential significant toxicities associated with the combination arm.

Disclosures

Dr Grothey's institution has received honoraria for consulting activities from Bayer, Roche/Genentech, Array, Boston Biomedical, and Caris. He has received travel support from Bayer, Roche/Genentech, and Array. Dr Marshall has received funds from Genentech, Bayer, Amgen, Taiho, Ipsen, Celgene, and Caris. Dr Bekaii-Saab is a consultant for AbbVie, Armo, SillaJen, Imugene, and Immuneering.

References

1. Tsuji Y, Shitara K, Yamanaka T, et al. REVERCE: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan—biomarker analysis [ASCO abstract 3510]. *J Clin Oncol*. 2018;36(15 suppl).
2. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer*. 2015;51(11):1405-1414.
3. Bekaii-Saab TS, Ou FS, Anderson DM, et al. Regorafenib dose optimization study (ReDOS): a phase II randomized study of lower dose regorafenib compared to standard dose regorafenib in patients with refractory metastatic colorectal cancer (mCRC) [ASCO abstract 611]. *J Clin Oncol*. 2018;36(suppl 4S).
4. Bendell J, Ciardiello F, Tabernero J, et al. Efficacy and safety results from IMblaze370, a randomised phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer [ESMO GI abstract LBA-004]. *Ann Oncol*. 2018;29(suppl 5).
5. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.

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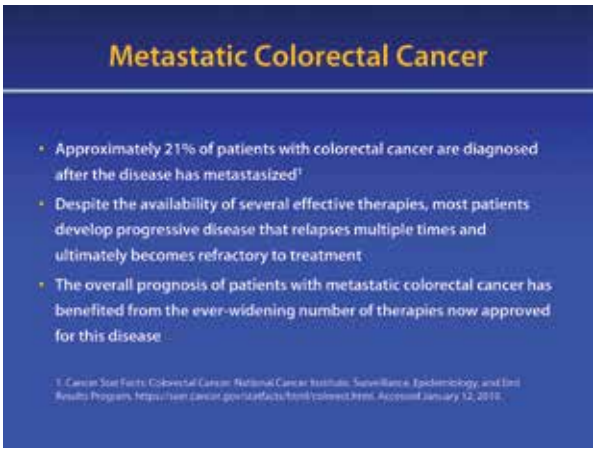

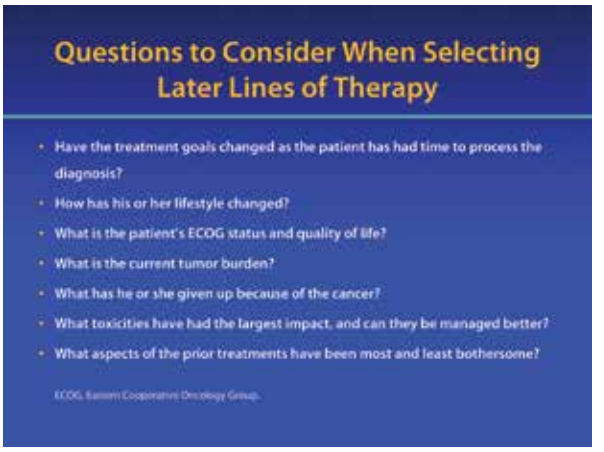

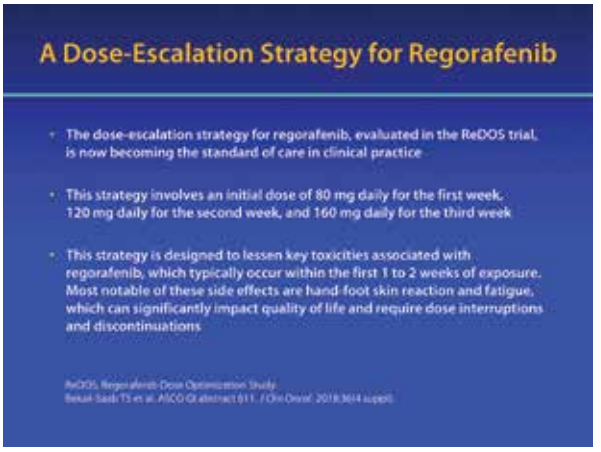

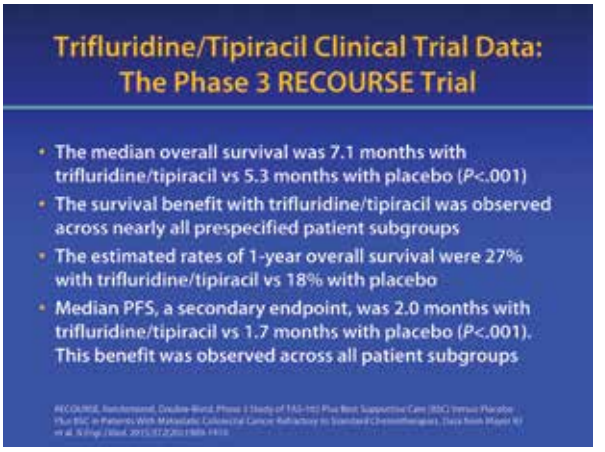

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