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Optimizing the Treatment Sequence From Second-Line to Third-Line Therapy in Patients With Metastatic Colorectal Cancer

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Abstract: In clinical trials of metastatic colorectal cancer, progressive disease after second-line therapy is often defined according to Response Evaluation Criteria in Solid Tumors criteria. In the clinic, however, disease progression can be identified through a composite of factors, including new lesions, carcinoembryonic antigen level, and symptoms such as pain and fatigue. It is optimal to switch to third-line treatment before the patient's performance status deteriorates. In the third-line setting, regorafenib and trifluridine tipiracil are approved for the treatment of patients with metastatic colorectal cancer who are refractory to standard chemotherapy. Both of these treatments are associated with prolonged overall survival and progression-free survival in heavily pretreated patients. Data suggest that a chemotherapy break may be beneficial in patients with metastatic colorectal cancer. Some data suggest that treatments beyond the third-line setting might also improve outcome.

Identifying Disease Progression in Patients With Metastatic Colorectal Cancer: When to Initiate Third-Line Therapy

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First-Line and Second-Line Therapy in mCRC

The goals of care in metastatic colorectal cancer (mCRC) are primarily palliative, with the intent to prolong survival and maintain the patient's quality of life. There are now several therapies available for the first-line and second-line treatment of mCRC. These treatments are associated with improvements in progression-free survival (PFS) and overall survival, as well as tumor response.[1-3] Tumor response is highest in the first-line setting, ranging from approximately 30% to more than 60% in certain groups.[4] In the second-line setting, tumor response decreases to 5% to 10%.

Treatment selection will be based on the molecular characteristics of the disease in a particular patient. Some of the most important molecular classifications that drive treatment decisions include whether the disease is *RAS* wild-type or *RAS* mutated, if it is *BRAF* wild-type or *BRAF* mutated, or whether it has human epidermal growth factor receptor 2 (*HER2*) amplification (which would exclude those patients from receiving epidermal growth factor receptor [EGFR] inhibitor therapies during the first-line or second-line settings).

Another important consideration when deciding on treatment in the first-line and second-line setting is whether the patient has left-sided vs right-sided disease. Evidence shows that patients with right-sided tumors have the worst outcomes. They do not respond to EGFR inhibitor therapy even if it appears they should according to molecular classification. A high degree of microsatellite instability can also be used to drive treatment decisions, both upfront and in later lines of therapy.

Initial treatment options for mCRC rely primarily on combination chemotherapy regimens, typically fluorouracil, irinotecan, and oxaliplatin. Bevacizumab, which targets vascular endothelial growth factor (VEGF), is often combined with chemotherapy in the first-line setting.

In my practice, patients with right-sided tumors, regardless of the genetic profile, are primarily treated with first-line leucovorin, fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) administered with or without bevacizumab. Patients who are unable to tolerate this regimen receive a chemotherapy doublet. The molecular status is a larger consideration for patients with left-sided tumors. Patients who are *RAS* wild-type, *BRAF* wild-type, who do not have the HER2 amplification, and who have microsatellite stability typically receive either leucovorin, fluorouracil, and oxaliplatin (FOLFOX) or leucovorin, fluorouracil, and irinotecan (FOLFIRI) plus bevacizumab. EGFR inhibitor agents would be acceptable alternatives to VEGF inhibitors in this group of patients.

Maintenance therapy should be considered in all patients who receive doublet or triplet chemotherapy in the first-line setting. In our practice, we consider maintenance capecitabine plus bevacizumab for all patients treated with 3 or 4 months of intensive first-line chemotherapy. Multiple studies have now established that these patients show similar or better outcomes with maintenance therapy, as opposed to continuing aggressive first-line treatment until

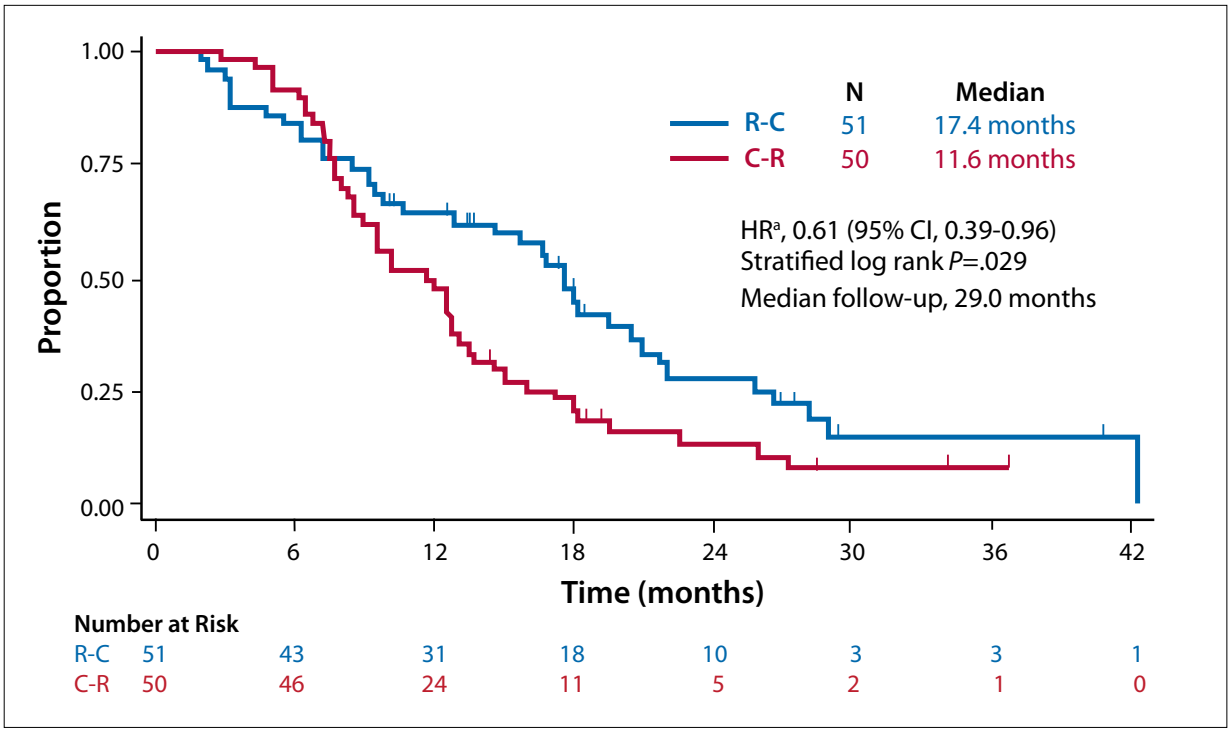

Figure 1. In the phase 2 REVERCE trial, overall survival was improved with the sequence of regorafenib followed by cetuximab (R-C) vs the sequence of cetuximab followed by regorafenib (C-R). [a]Adjusted by intent to use irinotecan. HR, hazard ratio; REVERCE, Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan. Adapted from Shitara K et al. *Ann Oncol.* 2019;30(2):259-265.[10]

unacceptable toxicity or disease progression.[5]

Treatment choice in the second-line setting becomes more complicated. It is recommended that all patients undergo molecular profiling for both microsatellite instability and for alterations in genes, including *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations, *HER2* amplifications, and *NTRK* fusions. Approximately 50% of patients have *RAS/BRAF* wild-type tumors.[6] Molecular testing is critical, as it is an important driver for therapeutic decisions. For example, patients with *RAS/BRAF* wild-type mCRC and a left-sided tumor benefit most from treatment with EGFR-targeted agents (such as panitumumab and cetuximab).[7] However, EGFR-targeted agents may actually be harmful, or at least ineffective, in patients with *RAS* mutations.[8,9]

EGFR inhibitors are generally reserved for the second-line or even third-line setting, based on their propensity for associated toxicities, such as rash and diarrhea.[9] Conversely, anti-EGFR therapy may be used in the first-line setting, and VEGF-targeted agents are instead relied upon in the second-line setting and beyond.

For a patient with right-sided disease who was treated with FOLFOXIRI plus bevacizumab in the first-line setting, my choice in the second-line setting would be to avoid further chemotherapy and instead proceed to either regorafenib or trifluridine/tipiracil. Regorafenib is a multikinase inhibitor targeting multiple facets of the tumor and the microenvironment. Trifluridine/tipiracil is a cytotoxic agent that belongs to the superfamily of fluoropyrimidines. In my practice, I prefer to start with regorafenib over trifluridine/tipiracil primarily based on the mounting evidence that regorafenib has increased activity in earlier lines of therapy vs later lines of therapy (when patients tend to benefit to a lesser degree). In contrast, trifluridine/tipiracil seems to preserve its activity even in the later lines of treatment.

One example of the evidence suggesting a benefit with introducing regorafenib earlier in the course of treatment comes from the REVERCE trial (A Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Previously Treated Metastatic Colorectal Cancer Patients).[10] This phase 2 study (discussed in more detail in a later section) evaluated the use of regorafenib administered before or after cetuximab. The study was small (N=101) and stopped early based on lack of funding. However, it showed a statistically significant benefit in the primary endpoint of overall survival with the sequence of regorafenib followed by cetuximab vs the sequence of cetuximab followed by regorafenib (median overall survival, 17.4 vs 11.6 months, respectively; hazard

ratio [HR], 0.61; 95% CI, 0.39-0.96; *P*=.0293; Figure 1).

Second-line treatment for left-sided tumors presents a different challenge. For patients with left-sided tumors that are both *RAS* and *BRAF* wild-type, choices for second-line treatment are generally either FOLFOX or FOLFIRI (whichever regimen was not used in the first-line setting), plus a VEGF or EGFR inhibitor. In my practice, I will often switch the biologic in the second line. For example, a patient treated with FOLFIRI plus bevacizumab in the first-line setting would receive either FOLFOX plus panitumumab or FOLFOX plus cetuximab.

Patients with left-sided tumors whose disease shows *HER2* amplification do not benefit from EGFR inhibitor agents. Instead, options for dual HER2-targeted therapies include trastuzumab plus pertuzumab or trastuzumab plus lapatinib.

The investigational small molecule HER2 inhibitor tucatinib showed activity when combined with trastuzumab in the second-line setting in the multicenter, open-label, single-arm phase 2 MOUNTAINEER trial (A Phase II, Open Label Study of Tucatinib Combined With Trastuzumab in Patients With HER2+ Metastatic Colorectal Cancer).[11] This trial enrolled 26 patients with *RAS* wild-type and *HER2*-amplified mCRC. Among the 23 evaluable patients, the overall response rate (ORR) was 52%, which includes 12 patients who achieved either a complete or partial response.[11] In addition, 6 patients developed stable disease (clinical benefit rate, 64%). The median duration of response had not been reached at the time of the analysis. The median PFS was 8.1 months (95% CI, 3.8 to not estimable), and the median overall survival was 18.7 months (95% CI, 12.3 to not estimable). Grade 3 treatment-related adverse events (AEs) were reported in 2 patients; no grade 4 or 5 events were reported.

For the group of patients with *BRAF* V600E mCRC (who tend to also have *RAS* wild-type and left-sided disease) who received FOLFOXIRI plus bevacizumab in the first line, the regimen used in the global, multicenter, randomized, open-label, phase 3 BEACON CRC trial (Binimetinib, Encorafenib, and Cetuximab Combined to Treat *BRAF*-Mutant Colorectal Cancer) presents the best option for second-line treatment.[12] This trial enrolled patients with confirmed mCRC that was positive for a *BRAF* V600E mutation and who had disease progression following 1 or 2 prior lines of treatment. Treatment consisted of triplet therapy with the BRAF inhibitor encorafenib, the MEK inhibitor binimetinib, and the EGFR inhibitor cetuximab (n=224); doublet therapy with encorafenib and cetuximab (n=220); or the investigator's choice of control treatment that consisted of either cetuximab plus irinotecan or cetuximab plus FOLFIRI (n=221).

At the interim analysis, the median overall survival was significantly longer with triplet therapy vs the control therapy (9.0 vs 5.4 months; HR, 0.52; 95% CI, 0.39-0.70; *P*<.001), meeting the primary endpoint. The median overall survival was 8.4 months in the doublet therapy arm, which was also significantly longer as compared with the control arm (HR, 0.60; 95% CI, 0.45-0.79; *P*<.001). The independently assessed ORR was significantly higher in the triplet therapy group compared with the control group (26% vs 2%; *P*<.001), as was the doublet therapy group (20%; *P*<.001). Median PFS was longer in both the triplet therapy arm (4.3 months) and doublet therapy arm (4.2 months) vs the control arm (1.5 months).

Grade 3 or higher AEs occurred in 58%, 50%, and 61% of patients receiving triplet therapy, doublet therapy, or control therapy, respectively. Rash is a noted toxicity of these agents when used individually. Interestingly, the rate of rash was not particularly high, at 19% with triplet therapy, 12% with doublet therapy, and 14% with control therapy.

Community Views on Disease Progression

Clinical trials define progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In the clinic, however, identifying disease progression is based on a composite of factors. Assessment is not solely based on factors such as the presence of a new lesion or an increase in the carcinoembryonic antigen (CEA) level. In addition to new lesions and CEA level, other factors to consider are molecular markers and the location (ie, "sidedness") of the disease. For example, the index for progression may need to be lower in patients with the *BRAF* V600E mutation, who often develop quickly progressive disease and can deteriorate rapidly. In mCRC, the diagnosis of disease progression is also often made if the patient becomes symptomatic.

As an example, a patient might begin to suddenly feel more pain or report additional cancer-related symptoms, such as fatigue and anorexia. The physician might then order a blood test to determine CEA levels. Elevated CEA can indicate progressive disease, and the physician would then order an imaging scan. A computed tomography scan might show vague tumors in the liver that appear new and could be indicative of progression. These factors, when taken together, begin to resemble progressive disease.

In some cases, patients who begin to show a sign of progression in isolation (eg, CEA elevation) are immediately switched to their next line of chemotherapy. Although this strategy is not necessarily wrong, it is not best practice, particularly if the scan shows no new disease and the patient feels well.

Third-Line Treatment Options

In the third-line setting, after a patient has received combination chemotherapy regimens with fluorouracil, oxaliplatin, irinotecan, VEGF-targeted agents, and, when indicated, EGFR-targeted agents, there are 2 treatments

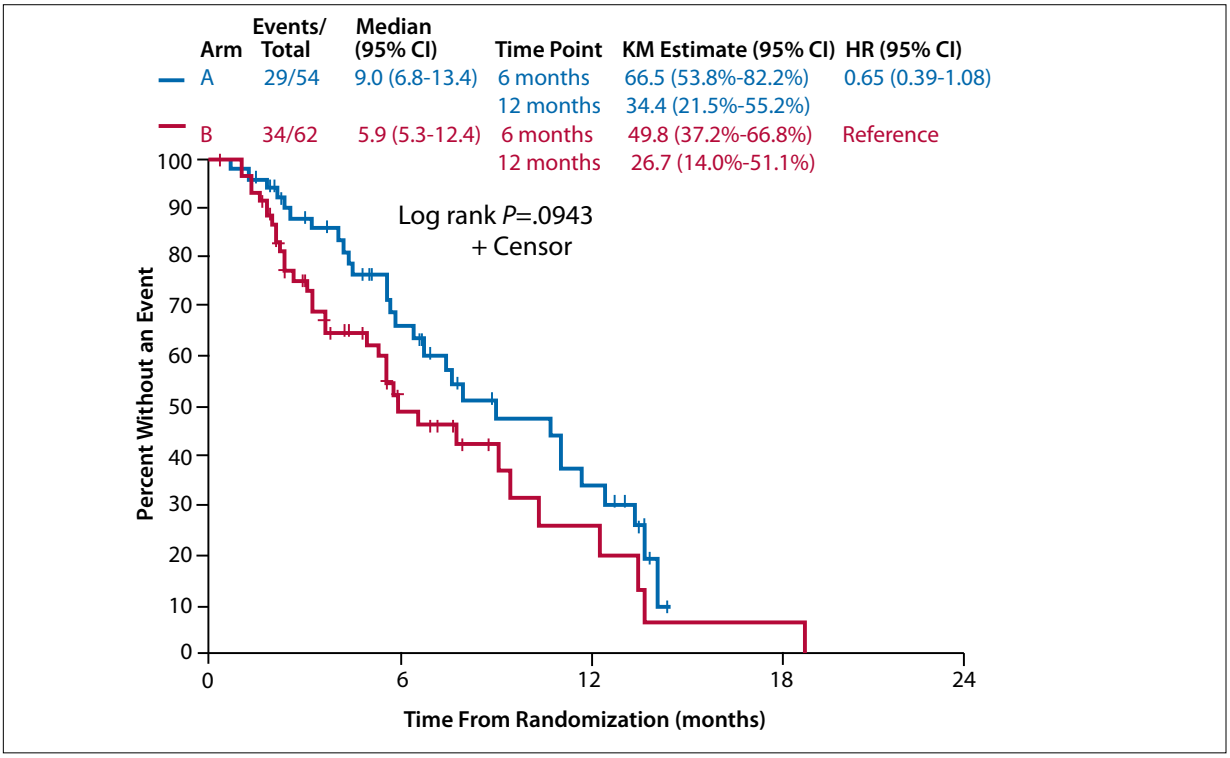

Figure 2. Overall survival in the phase 2 ReDOS trial, which compared a fixed dose of regorafenib vs a dose-escalated regimen. Patients in arm A received regorafenib at 80 mg/day, with weekly dose escalation up to 160 mg/day in the absence of significant drug-related toxicities. In arm B, patients received the standard dose of regorafenib at 160 mg/day. ReDOS, Regorafenib Dose Optimization Study. Adapted from Bekaii-Saab TS et al. *Lancet Oncol*. 2019;20(8):1070-1082.[15]

approved by the FDA: regorafenib and trifluridine/tipiracil.[13,14] Both of these oral agents are associated with prolonged overall survival and PFS in heavily pretreated patients. It is important to realize that although these agents do not necessarily induce a significant tumor response, they do indeed improve survival. For some patients, this prolonged overall survival is not insignificant, and can extend beyond 1 year (Figure 2).[15]

Additionally, newly available agents now mean that a deeper molecular profile is necessary. For example, patients with a high degree of microsatellite instability or mismatch repair–deficient mCRC are candidates for the checkpoint inhibitors pembrolizumab or nivolumab.[16,17] Patients should also be tested for the presence of *NTRK* fusions. Although rare, this molecular abnormality can now be effectively targeted with the NTRK inhibitors larotrectinib and entrectinib, which are associated with robust tumor responses in *NTRK* fusion–positive cancers.[18,19]

Benefits to Switching From Second-Line Therapy

Switching treatment is always best reserved when done for the benefit of the patient who is actually deemed to be progressing. Patients are switched from second-line to third-line and fourth-line treatments given that we have agents available to us that have been proven to prolong survival in this setting: regorafenib and trifluridine/tipiracil. For the right patients who will benefit from this switch, it should be done sooner rather than later, before performance status begins to significantly deteriorate. Thus, it is important to remember this goal and follow the patient closely as they progress through lines of therapy to catch them before they deteriorate beyond salvage.

Potential Benefits of a Chemotherapy Break

Several studies published over the past 2 decades have set the stage to suggest that a chemotherapy break may be beneficial in patients with mCRC. For example, a randomized study of 354 patients who were randomly assigned to either intermittent or continuous chemotherapy showed no clear evidence of a benefit in continuing therapy indefinitely until disease progression. Instead, these data showed that it is safe to stop chemotherapy after 12 weeks and re-start the same treatment on disease progression.[20] In a separate pooled analysis from 3 consecutive randomized controlled trials, a multivariate analysis found that a prolonged treatment-free interval exceeding 12 months was associated with better overall survival compared with prolonged treatment (HR, 0.57; 95% CI, 0.35-0.94; *P*=.027). The incidence of toxicity related to fluorouracil was decreased during rechallenge vs initial treatment (Table 1). The authors of this pooled

Table 1. Incidence of Toxicity Related to 5-FU During the First and Second Treatment Courses

Toxicity	First Treatment (n=93)	Second Treatment (n=93)	*P* Value
Diarrhea			
All grades	48 (52%)	34 (37%)	.039
Grades 3/4	6 (6%)	3 (3%)	
Stomatitis			
All grades	53 (57%)	51 (55%)	.86
Grades 3/4	6 (6%)	3 (3%)	
Hand-foot syndrome			
All grades	83 (89%)	65 (70%)	.005
Grade 3	16 (17%)	9 (10%)	

5-FU, 5-fluorouracil.

Data from Yeoh C et al. *Clin Colorectal Cancer*. 2003;3(2):102-107.[21]

analysis concluded that a proportion of patients who experienced a prolonged period of tumor control with first-line 5-fluorouracil followed by a planned treatment interruption, retained 5-fluorouracil sensitivity and had prolonged survival with 5-fluorouracil rechallenge.[21] There are multiple benefits for maintenance or break, including the capacity to pursue sequential aggressive therapy while maintaining quality of life. There is also lower likelihood for end-organ damage, which again allows for maximal exposure to sequential therapy. Overall, treatment of metastatic colorectal cancer can be considered similar to a marathon rather than a sprint.

It is worthwhile to consider that the effectiveness of cytotoxic therapy itself diminishes when the patient progresses from first-line to second-line treatment. This was shown in the ML18147 study (A Randomized, Open-Label Phase III Intergroup Study: Effect of Adding Bevacizumab to Cross Over Fluoropyrimidine Based Chemotherapy [CTx] in Patients With Metastatic Colorectal Cancer and Disease Progression Under First-Line Standard CTx/Bevacizumab Combination), which showed that the ORR for FOLFOX or FOLFIRI in the second-line was at most 4%, with a median PFS of less than 2 months.[22]

Some observational data suggest that in patients who move from chemotherapy to a multikinase inhibitor such as regorafenib, subsequent treatment with chemotherapy may lead to a response.[23,24] There is a question of whether these patients truly progressed on chemotherapy before they switched to regorafenib. Overall, however, there appear to be benefits with stopping chemotherapy at some point. Some patients may respond to re-treatment with chemotherapy. This area requires further study.

Disclosure

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Refining the Use and Sequencing of Third-Line Therapy in Patients With Metastatic Colorectal Cancer

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Clinical Trial Data for Regorafenib

The CORRECT Trial

The CORRECT trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was a randomized, double-blind, placebo-controlled, phase 3 clinical trial designed to assess the efficacy and safety of regorafenib in patients with mCRC whose disease had progressed following treatment with all standard therapies approved at the time.[1] This international study enrolled patients from 114 centers across 16 countries throughout North America, Europe, Asia, and Australia. Given the international design, available standard therapies varied from country to country 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). The primary endpoint of the CORRECT study was overall survival; secondary endpoints included PFS, ORR, disease control rate, and safety. Tumor response and progression were assessed by the investigator every 8 weeks according to RECIST v1.1.

Enrolled patients had documented adenocarcinoma of the colon or rectum, and had received locally and currently approved standard therapies. They developed disease progression during or within 3 months after the last administration of the last standard therapy. Patients were also eligible if they had stopped standard therapy after unacceptable toxicity. In addition, patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectance of at least 3 months, and adequate hematologic, hepatic, and renal function.

The trial arms consisted of single-agent regorafenib at 160 mg daily (n=505) or matching placebo (n=255). Patients in both arms also received best supportive care. Treatment was administered once daily for the first 3 weeks of each 4-week cycle until disease progression, death, unacceptable toxicity, withdrawal of consent, or physician decision. Patient crossover was not permitted. At the time of randomization, patients were stratified by several factors, including prior treatment with VEGF-targeting 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).

Overall, baseline characteristics were similar in the regorafenib and placebo arms. An exception was the proportion of patients with a *KRAS* mutation, which was lower in the regorafenib arm compared with the placebo arm (54% vs 62%, respectively). As expected, there was a low frequency of *BRAF* mutations (4% and 2%, respectively) in this population of patients, who had a good performance status even after receiving several lines of treatment. The median age in both arms was 61 years, and most patients were white and male. At baseline, 49% in the regorafenib arm and 47% in the placebo arm had received 4 or more prior systemic therapies.

The primary endpoint of overall survival was met in the CORRECT study. 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).[1] The overall survival benefit observed with regorafenib was consistent across all patient subgroups, with the exception of patients

with primary disease in the colon and rectum; however, this subgroup analysis was limited by patient numbers.

Median PFS, a secondary endpoint, was 1.9 months with regorafenib vs 1.7 months with placebo, with curves clearly separating after the median (HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001). No complete responses were observed. The ORR was 1.0% with regorafenib and 0.4% with placebo (*P*=.19). The disease control rate, which included patients who achieved a partial response or stable disease, was 41% with regorafenib vs 15% with placebo (*P*<.0001).

Adverse events leading to dose modification were reported in 67% of the regorafenib arm and 23% of the placebo arm. Of these, 38% of regorafenib-treated patients required a dose reduction, and 61% required a dose interruption. The most common AE of any grade reported among patients treated with regorafenib were fatigue and hand-foot skin reaction. Adverse events occurred most frequently during the first or second treatment cycle. Grade 1 or 2 increases in liver transaminases or bilirubin occurred more frequently with regorafenib than placebo. More patients who received regorafenib experienced a grade 3 or 4 treatment-related AE compared with placebo (54% vs 14%, respectively). The most frequent regorafenib-related AEs of grade 3 or higher were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation. Among the 110 deaths reported during the study, most were from disease progression. Eleven deaths were attributed to AEs (8 in the regorafenib arm and 3 in the placebo arm). The degree of deterioration in quality of life and health status was similar in both arms.

The CONCUR Study

Although the CORRECT study was an international study, just 111 of the 760 patients were Asian (90% of whom were Japanese).[1] Thus, the CONCUR study (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was designed to confirm the efficacy and safety of regorafenib in a broader population of Asian patients with refractory mCRC.[2] CONCUR was a similarly designed, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial conducted in 25 hospitals located throughout China, Hong Kong, South Korea, Taiwan, and Vietnam.

Like CORRECT, patients in the CONCUR trial had confirmed adenocarcinoma of the colon or rectum. Patients had received at least 2 prior lines of treatment, including a fluoropyrimidine plus oxaliplatin or irinotecan. One difference in the design of the CONCUR study was that it permitted enrollment of patients who had not been treated with a biologic agent, owing to the limited availability of these drugs in some Asian countries at the time of the trial. Among the overall study population, 40% had not previously received any targeted biologic agent prior to the study. Other eligibility criteria were similar to the CORRECT study.

The trial arms consisted of regorafenib at 160 mg (n=136) and matching placebo (n=68). Best supportive care was also administered in both arms. Treatment was administered once daily for the first 21 days of each 28-day treatment cycle until disease progression, death, unacceptable toxicity, withdrawal of consent, or decision by the treating physician. Patients were stratified by the number of metastatic sites (single vs multiple organs) and time from diagnosis of metastatic disease (<18 months vs ≥18 months). Overall survival was the primary endpoint. PFS, ORR, and disease control rate were secondary endpoints. Tumor response and progression were assessed by the investigator every 8 weeks according to RECIST v1.1.

At baseline, 63% of the study population had received 3 or more lines of treatment for mCRC.[2] Patients in the CONCUR trial were slightly younger (median age, 56.5 years) compared with the CORRECT trial. A *KRAS* mutation was present in 34% of patients in the regorafenib arm and 26% of patients in the placebo arm. A *BRAF* mutation was identified in 1 patient (in the placebo arm). 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 overall survival was met. 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 3).[2] An exploratory analysis of the effect of previous targeted biologic treatment found that the HR for overall survival was 0.31 (95% CI, 0.19-0.53) in patients who had not previously received targeted treatment. The HR for overall survival was 0.78 (95% CI, 0.51-1.19) in patients who had received at least 1 targeted biologic agent. The data thus suggested that the survival benefit associated with regorafenib was larger in less heavily pretreated patients, in particular with regard to prior biologic agents. Median PFS, a secondary endpoint, was also significantly improved with regorafenib compared with placebo (3.2 vs 1.7 months; HR, 0.31; 95% CI, 0.22-0.44; 1-sided *P*<.0001). Prespecified subgroup analyses of both overall survival and PFS demonstrated that the benefit associated with regorafenib was consistent across nearly all patient subgroups.

The ORR was 4% with regorafenib and 0% with placebo (1-sided *P*=.045); all responses were partial.[2] More patients in the regorafenib arm achieved disease control (a partial response or stable disease) than in the placebo arm (51% vs 7%, respectively; 1-sided *P*<.0001). The median duration of response among the regorafenib-treated patients with a partial response was 4.8 months (interquartile range [IQR], 3.8-14.4). The median duration of response was 3.0 months (IQR, 1.8-5.6) with regorafenib and 1.7 months (IQR, 1.4-1.9) with placebo.

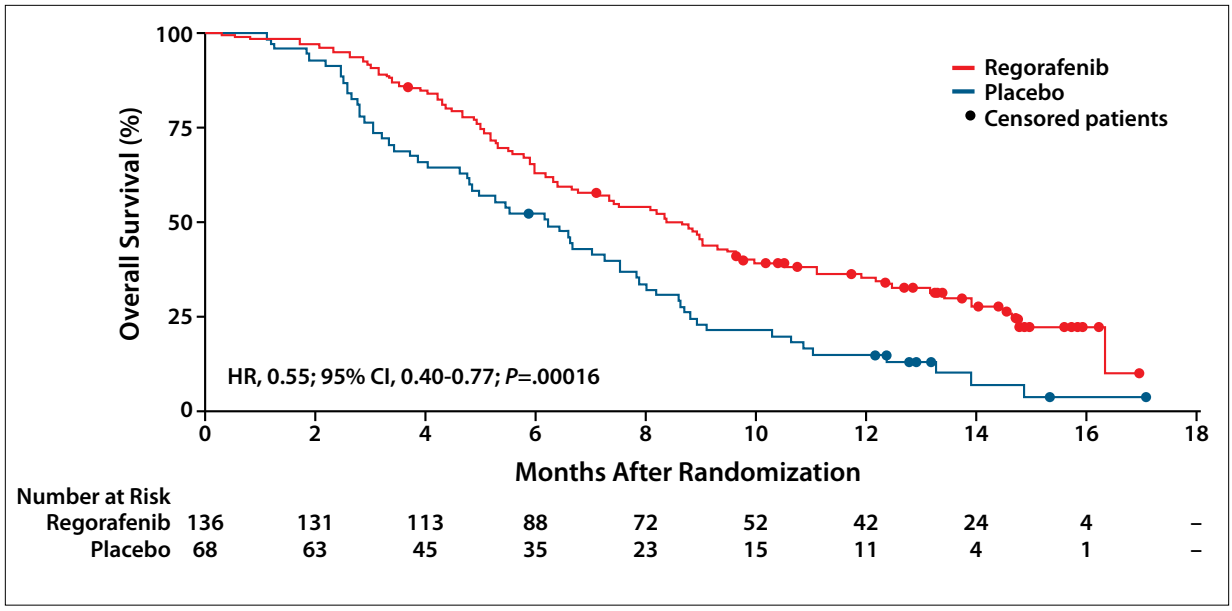

Figure 3. Median overall survival in the phase 3 CONCUR trial of regorafenib vs placebo. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.[2]

Grade 3 or higher AEs considered treatment-related occurred in 54% of the regorafenib arm and 15% of the placebo arm. The most frequent grade 3 or higher treatment-related AEs were hand-foot skin reaction, hypertension, hyperbilirubinemia, hypophosphatemia, alanine aminotransferase concentration increase, aspartate aminotransferase concentration increase, lipase concentration increase, and maculopapular rash. Two deaths were attributed to treatment with regorafenib.

Adverse events led to treatment discontinuation in 14% of the regorafenib group and 6% of the placebo group. The most common AEs leading to discontinuation were laboratory events. Treatment modification (treatment interruption, dose reduction, or both) was attributed to AEs in 71% of regorafenib-treated patients and 16% of placebo-treated patients. Patient quality of life and health status deteriorated to a similar extent in both treatment groups.

The IMblaze370 Study

IMblaze370 (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma) was an international, multicenter, open-label, phase 3, randomized controlled trial that utilized regorafenib as the standard of care in the comparator arm.[3] The trial was initiated in view of preliminary data from a single-arm, phase 1b study that showed a surprising 20% ORR in patients with microsatellite stable mCRC with the atezolizumab/cobimetinib combination.[4] Patients with predominantly microsatellite-stable unresectable mCRC had received previous treatment with fluoropyrimidine, oxaliplatin, and irinotecan and had developed progressive disease or were intolerant to therapy. All patients had a baseline ECOG performance status of 0 or 1, a life expectancy of 3 months or more, and adequate hematologic and end-organ function.

Patients were randomly assigned into 3 treatment arms to receive the programmed death ligand 1 (PD-L1) checkpoint inhibitor atezolizumab administered at 840 mg every 2 weeks, plus the MEK1/MEK2 inhibitor cobimetinib at 60 mg administered once daily for days 1 to 21 of a 28-day cycle (n=183), atezolizumab monotherapy administered at 1200 mg every 3 weeks (n=90), or single-agent regorafenib 160 mg administered once daily for days 1 to 21 of a 28-day cycle (n=90).

The primary endpoint of overall survival was not met in the IMblaze370 trial.[3] Overall survival did not differ significantly among any of the treatment groups. Median overall survival was 8.87 months with atezolizumab plus cobimetinib, 7.10 months with atezolizumab monotherapy, and 8.51 months with regorafenib. The stratified HR was 1.00 (95% CI, 0.73-1.38; *P*=.99) for atezolizumab plus cobimetinib vs regorafenib and 1.19 (0.83-1.71; *P*=.34 [for descriptive purposes only]) for atezolizumab monotherapy vs regorafenib. Median PFS was also not significantly different among the treatment groups, at 1.91 months in the combination group, 1.94 months in the atezolizumab group, and 2.00 months in the regorafenib group.

Regorafenib was chosen as the standard of care in the comparator arm because it is approved globally in

the treatment setting tested in the study. Notably, in this randomized IMblaze370 trial, patients in the regorafenib group survived longer than the protocol assumption of 6.4 months, which was based on the CORRECT study.[1,3]

Real-World Analyses of Regorafenib

The CORRELATE Study

The CORRELATE study (Safety and Effectiveness of Regorafenib in Routine Clinical Practice Settings) was a prospective, observational cohort study designed to characterize the safety and effectiveness of regorafenib in an unselected, real-world population of patients with mCRC who were treated in routine clinical practice settings.[5,6] This study was conducted across 126 centers throughout Europe, Asia, and Latin America. The study population consisted of patients with mCRC who were previously treated with, or who were not considered candidates for, other approved therapies and were selected for treatment with regorafenib by the treating physician.

The primary objective of this study was to understand the safety of regorafenib in real-world practice, as assessed by treatment-emergent AEs reported during treatment through 30 days afterward. The secondary objective was to evaluate the efficacy of regorafenib in real-world practice, as determined by overall survival, PFS, and disease control rate. A total of 1037 patients were treated between April 2014 and July 2017 and were included in this analysis. The final analysis cut-off date was December 15, 2017.

Approximately half of the patient population was 65 years or older. The primary tumor site was the colon in 70% of patients, the rectum in 28%, and the colon and rectum in 2%. ECOG performance status was 0 or 1 in 87% of the population. A total of 39% of the population had received at least 4 prior systemic treatments.

Regorafenib was initiated at a dose of 160 mg in 57%, 120 mg in 30%, or 80 mg or less in 13%. Dose reductions were more common among patients who initiated treatment at the highest dose. However, the percentages of patients requiring a dose interruption, delay, or other modification were similar between the 160 mg and 120 mg initiation doses. Approximately half of patients (49%) discontinued treatment owing to radiologic disease progression, and 19% discontinued because of regorafenib-related treatment-emergent AEs.[6]

Patients were assessed according to the treating physician's routine practice.[5] 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%.

All-grade treatment-emergent AEs 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 AEs 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%).

The Japanese Post-Marketing Surveillance Study

A large, prospective, multicenter, observational postmarketing surveillance study evaluated the safety and efficacy of regorafenib for the treatment of mCRC in real-world conditions in a Japanese population.[7] The study included 1227 patients treated between March 2013 and May 2015. At baseline, the median age of the population was 65 years, and 59% were male. Most patients had an ECOG performance status of 0 (43.6%) or 1 (48.0%), and 51.2% had *KRAS* wild-type disease. Prior systemic therapies numbered 4 in 25.4%, 3 in 36.8%, and 1 or 2 in 37.8% of the population. Prior therapies included bevacizumab in 91.0%, panitumumab in 34.6%, and cetuximab in 27.7%.

The recommended dose of regorafenib was 160 mg once daily for the first 3 weeks of a 4-week cycle, based on the CORRECT trial.[1] Approximately two-thirds of patients initiated regorafenib at this dose (65.4%); the remaining patients initiated treatment at a daily dose of 120 mg (21.6%) or lower (13.0%). Dose modifications were permitted according to the regorafenib label.[8]

The median duration of treatment was 7.6 weeks (range, 0.1-86.3). A dose interruption was required by 49.3% of patients, and 42.1% required a dose reduction. Treatment was discontinued owing to an AE for which a causal relationship with regorafenib could not be excluded (an adverse drug reaction, abbreviated as ADR) in 33% of patients. Grade 3 or higher ADRs were reported in 51.8% of patients, and most often consisted of hand-foot skin reaction (19.2%), hypertension (15.6%), liver injury (11.5%), thrombocytopenia (4.7%), and decreased appetite (2.7%). The most common ADR of any grade was hand-foot skin reaction (58.2%), followed by liver injury (31.4%) and hypertension (28.8%).

A landmark analysis identified several factors with a significant effect on overall survival.[7] Factors associated with better overall survival included resection of the primary site, the presence of hand-foot skin reaction on day 28, and the rectum as the primary site of disease. Factors associated with worse overall survival included ascites, metastasis in the liver, metastasis in the bone, an ECOG performance status of 2 or higher, and a body surface area of less than 1.6 m^2.

The CORECT Registry

The Czech CORECT registry is a noninterventional postmarketing database for patients with CRC who were treated with targeted agents in clinical practice.[9] Twenty

oncology centers in the Czech Republic contributed to this registry. An analysis of 148 patients from the CORECT registry showed that nearly all patients were either fully active or slightly restricted in physical activity when they began regorafenib treatment. Median PFS was 3.5 months, and median overall survival was 9.3 months. At 1 year, 44.6% of patients were alive. Four patients achieved a partial response, 51 had stable disease, and 66 patients had disease progression. The primary AEs reported in this registry were skin toxicity (5.4%) and fatigue (2.0%).

Clinical Trial Data for Trifluridine/Tipiracil

The RECOURSE Study

The double-blind, randomized, phase 3 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) assessed the safety and efficacy of trifluridine/tipiracil in a broad patient population.[10] 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 were randomly assigned 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. Patients repeated treatment cycles up to 4 times. All patients in both arms also received best supportive care. At randomization, patients were stratified by *KRAS* status, the time from first diagnosis of metastasis, and geographic region.

Baseline characteristics were well balanced between the 2 treatment arms. The patients' median age was 63 years, and 61% were male. ECOG performance status was 0 in 56% and 1 in 44%. Most patients (61%) had received 4 or more prior therapies.

Overall survival, the primary endpoint, was reached in the RECOURSE study. The median overall survival was 7.1 months with trifluridine/tipiracil and 5.3 months with placebo (HR, 0.68; 95% CI, 0.58-0.81; *P*<.001). The improvement in overall survival achieved with trifluridine/tipiracil was observed across nearly all prespecified patient subgroups. 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%, respectively; *P*=.29). The disease control rate was significantly higher in the trifluridine/tipiracil arm as compared with the placebo arm (44% vs 16%, respectively; *P*<.001).

Treatment with trifluridine/tipiracil resulted in a significant delay in the worsening of ECOG performance status from baseline levels of 0 or 1 to 2 or higher.[10] 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).

Adverse events of grade 3 or higher were more frequent with trifluridine/tipiracil compared with 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 to develop grade 3 or higher nausea (2% vs 1%), vomiting (2% vs <1%), and diarrhea (3% vs <1%).

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) was a confirmatory trial that evaluated trifluridine/tipiracil in an Asian population with mCRC.[11] Overall, patients in this study had lower exposure to biologic agents than seen in the RECOURSE study. Patients from 30 sites across China, the Republic of Korea, and Thailand were randomly assigned to treatment with trifluridine/tipiracil (n=271) or placebo (n=135).

The median overall survival was 7.8 months with trifluridine/tipiracil vs 7.1 months with placebo. The risk of death was significantly lower 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. Unlike the data for regorafenib in CONCUR vs CORRECT, the magnitude of survival benefit reported in the TERRA study was historically similar to that reported in the RECOURSE trial.[1,2,10,11]

Real-World Analysis of Trifluridine/Tipiracil

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) evaluated the safety and efficacy of trifluridine/tipiracil in daily practice.[12] The study included 462 patients from 10 countries who had received at least 1 dose of treatment. The patients' median age was 64 years (range, 28-87), and 63.6% were male. More than 97% had received previous treatment with fluoropyrimidine, oxaliplatin, or irinotecan, and 96.3% had received oxaliplatin plus irinotecan. Other treatments included anti-VEGF therapy in 83.9%, anti-EGFR therapy in 41.5%, and regorafenib in 35.7%.

After at least 5 months of follow-up, the median treatment duration was 3 months (range, 0.5-11.0), and the median number of cycles was 3 (range, 1-12). At the

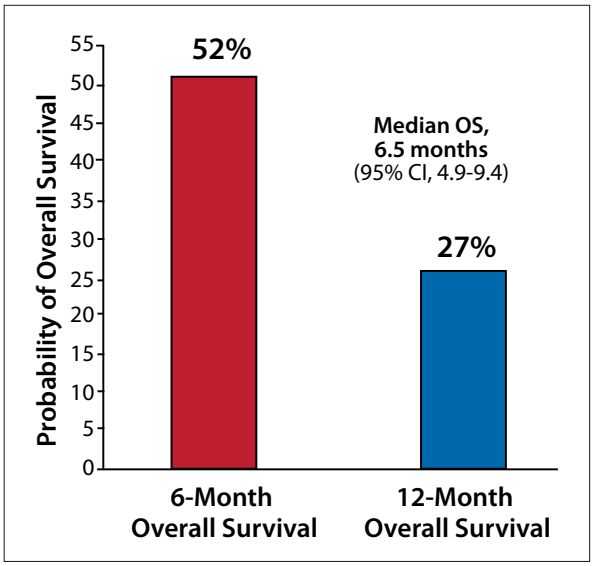

Figure 4. Overall survival after discontinuation of regorafenib in a retrospective review of case series of patients with metastatic colorectal cancer. Adapted from Kidd M et al. ASCO GI abstract 678. *J Clin Oncol.* 2015;33(3 suppl).[13]

time of data cutoff, 77.3% of patients had withdrawn from the study owing to progressive disease. Other reasons for study withdrawal included AEs in 6.7% and treatment-related AEs in 2.2%. Forty deaths occurred.

Among 414 patients who received trifluridine/tipiracil and underwent a postbaseline tumor evaluation, the median PFS was 2.8 months (95% CI, 2.7-3.3), and the disease control rate was 36.8% (95% CI, 32.4%-41.4%). The ORR was 2.4% (95% CI, 1.2%-4.2%). The median overall survival was not reached.

AEs were reported by 92.6% of patients. The median relative dose intensity was 89%. An AE required a dose reduction in 8% of patients; the most common reason was neutropenia (2.8%). Adverse events of grade 3 or higher were reported in 72.5% of patients; the most common grade 3 or higher events were neutropenia in 39.3%, anemia in 11.8%, and diarrhea in 5.2%. Febrile neutropenia was reported in 1.7% of patients. Drug-related AEs occurred in 74.5%. The most common drug-related AEs were neutropenia (49.5%), nausea (27.7%), and diarrhea (20.6%). AEs of grade 3 or higher related to treatment were reported in 48.6%. The most common of these events were neutropenia (38%) and anemia (7.1%). Nonhematologic grade 3 or higher treatment-related AEs included diarrhea (3.5%) and fatigue (2.2%). The median time to an ECOG performance status of 2 or higher was 8.7 months (range, 0.2-11.0).

Clinical Evidence for the Use of Regorafenib Before Chemotherapy Rechallenge

Kidd and colleagues conducted a multi-institution retrospective review of case series from patients with mCRC treated at Mayo Clinic, MD Anderson, or the University of Southern California.[13] This review analyzed the response to chemotherapy administered after regorafenib. Response and disease progression outcomes were determined by investigator review of imaging and clinical notes.

A total of 173 patients were identified. Of these, 11 patients (6%) were continuing treatment with regorafenib and 98 patients (57%) received no subsequent therapy. A total of 64 patients (37%) received treatment after regorafenib. Among these patients, 31 were treated in a phase 1 clinical trial, and 33 patients received a standard approved therapy. The latter patients were analyzed for response outcomes. Twenty of these patients had a partial response or stable disease (61%) and 11 developed disease progression (33%). (Two patients [6%] were not evaluable.) The median overall survival for patients who received a standard agent after regorafenib was 6.5 months (95% CI, 4.9-9.4).[11] The probability of survival decreased steadily with increasing time after discontinuation of regorafenib, and was 72% at 3 months, 52% at 6 months, and 27% at 12 months (Figure 4).

The authors of this collaborative retrospective review concluded that further treatment after regorafenib could be considered in appropriate patients. In some cases, patients responded to a treatment they had already received in an earlier line of therapy.

A retrospective study by Tai and colleagues compared the efficacy of different sequencing regimens of regorafenib and reduced-intensity FOLFOXIRI in mCRC.[14] Specifically, a regorafenib-first strategy (n=136) was compared against a reduced-intensity FOLFOXIRI (riFOLFOXIRI)-first strategy (n=55), with the goal to determine if one approach provided a survival advantage in the treatment of refractory mCRC. This single-center retrospective cohort study included patients treated between August 2012 and January 2018 in a Taiwanese hospital. Patients were refractory to treatment with cetuximab (if they had wild-type *RAS* disease), bevacizumab, irinotecan, oxaliplatin, and fluorouracil.

Among the 136 patients assigned to the regorafenib-first strategy, 41 (30.1%) switched to subsequent riFOLFOXIRI, while 95 patients (69.9%) received only regorafenib. Among the 55 patients assigned to the riFOLFOXIRI-first strategy, 47 (85.5%) went on to switch to subsequent regorafenib, and 8 patients (14.5%) received only riFOLFOXIRI. A total of 58.5% of patients in the regorafenib-first group initiated regorafenib at a dose of 120 mg daily, and 68.1% initiated regorafenib at a dose of 120 mg daily in the riFOLFOXIRI-first group.

Patients assigned to the riFOLFOXIRI-first group were younger than those assigned to the regorafenib-first group (57.3 vs 65.8 years; $P<.001$). Other baseline characteristics, including body mass index, ECOG

Table 2. Responses to Different Sequences in a Study of Regorafenib and Reduced-Intensity FOLFOXIRI

	n (%)		*P* Value
	Regorafenib First (n=136)	**riFOLFOXIRI First (n=55)**	
Best response during treatment course			
Progressive disease	73 (53.7)	26 (47.3)	.005[a]
Stable disease	52 (38.2)	14 (25.5)	
Partial response	4 (2.9)	6 (10.9)	
Not accessible	7 (5.1)	9 (16.4)	
Reasons for treatment discontinuation			
Progressive disease	115 (84.6)	43 (78.2)	.004[a]
Adverse effect	8 (5.9)	11 (20)	
Ongoing treatment[b]	13 (9.6)	1 (1.8)	
Follow-up time (mean ± SD) (months)	12 ± 10.7	12.5 ± 10.6	.683

[a]*P*<.05.

[b]Number of patients in ongoing treatment at last follow-up.

riFOLFOXIRI, reduced-intensity leucovorin, fluorouracil, oxaliplatin, and irinotecan; SD, standard deviation.

Adapted from Tai CC et al. *Am J Clin Oncol.* 2020;43(1):28-34.[14]

performance status, disease stage, and *RAS* mutation status, did not differ significantly between the 2 groups.

Patients in the regorafenib-first group experienced a significant overall survival benefit compared with the riFOLFOXIRI-first group. The median overall survival was 13.8 vs 10.7 months, respectively (HR, 0.67; *P*=.038).[14] Median PFS was 4.97 months in the riFOLFOXIRI-first group vs 3.17 months in the regorafenib-first group, a difference that did not achieve statistical significance (HR, 0.916; *P*=.622). The rate of partial response was higher with the riFOLFOXIRI-first strategy (10.9% vs 2.9% in the regorafenib-first group), whereas the rate of stable disease was higher with the regorafenib-first strategy (38.2% vs 25.5% in the riFOLFOXIRI-first group). Overall, the median duration from the date of first detected metastasis to the date of death or loss to follow-up was 33.5 months for the entire patient population. This duration was significantly longer among patients in the regorafenib-first group compared with patients in the riFOLFOXIRI-first group (36.5 vs 27.8 months; *P*=.004).

A subgroup analysis aimed to identify patient and disease characteristics associated with the best outcomes in the regorafenib-first group.[14] Patients with the following characteristics were favored in the regorafenib-first treatment sequence: younger age (<70 years), ECOG performance status of 0, initial stage IV according to criteria from the American Joint Committee on Cancer, pathologic diagnosis of adenocarcinoma, and presence of the *RAS* gene mutation.

Significantly more patients discontinued treatment owing to progressive disease in the regorafenib-first group vs the riFOLFOXIRI-first group (84.6% vs 78.2%; *P*=.004; Table 2). More patients in the riFOLFOXIRI-first group discontinued treatment owing to intolerable adverse effects (20% vs 5.9%).

The study authors concluded that these data demonstrated that a regorafenib-first strategy provides a survival benefit, despite the lack of a PFS benefit and lower partial response rate compared with the riFOLFOXIRI-first strategy.[14] Although patients in the riFOLFOXIRI-first group achieved a better partial response rate, they had only a marginally better PFS, and the benefit in the partial response rate did not translate into a better overall survival.

Disclosure

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Use of Regorafenib Before Re-Challenging With Chemotherapy-Based Regimens in Patients With Metastatic Colorectal Cancer: Mechanistic Rationale

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Mechanism of Action of Regorafenib

Regorafenib is an oral, multitargeted tyrosine kinase inhibitor that targets different normal cellular functions and pathologic processes to combat tumors. The mechanism of action of regorafenib can be thought of as a 4-pronged strategy (Table 3). First, regorafenib blocks tumor angiogenesis primarily by targeting key angiogenic receptors: VEGF receptors (VEGFRs) 1, 2, and 3; TIE2; platelet-derived growth factor receptors (PDGFRs) α and β; and fibroblast growth factor receptors (FGFRs) 1 and 2.[1-3] Second, regorafenib blocks metastasis through inhibition of VEGFR 2 and 3, important mediators involved in endothelial cell proliferation and migration.[2,4] PDGFR, believed to play a role in cancer-associated, fibroblast-induced metastasis, is also inhibited by regorafenib.[5] Third, regorafenib disrupts tumor immunity by inhibiting colony stimulating factor 1 receptor (CSF1R), a receptor important for macrophage proliferation.[6] Fourth, regorafenib potently blocks multiple protein kinases, including KIT, RAF-1, and RET, enzymes that are important in oncogenesis.[1,2]

New Insights Into Regorafenib's Mechanism of Action

As was previously discussed, regorafenib directly targets the tumor microenvironment through inhibition of multiple tyrosine kinases. Recent studies have furthered our understanding of other mechanisms by which regorafenib may act. One strategy may be through stimulating the immune system. Data show that regorafenib can positively interfere with the immunosuppressive state, increasing the immunosensitivity of the tumor or the tumor microenvironment.

One way in which regorafenib may affect the immune system is via VEGFR inhibition. VEGF-induced angiogenesis results in abnormal tumor vasculature, leading to hypoxic-related effects that in turn create an immunosuppressive tumor microenvironment. VEGF is the major angiogenic growth factor, and it is also produced by several different immune cells. Increased VEGF directly inhibits trafficking, proliferation, and effector functioning of cytotoxic T lymphocytes. VEGF also inhibits dendritic cell maturation and antigen presentation, further diminishing T-cell activation and the T cell-mediated anticancer immune response. High VEGF expression can promote the recruitment and proliferation of immunosuppressive cells, including regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages.[7]

Regorafenib may also impact immune mechanisms by blocking angiopoietin 2 (ANG2) signaling. In addition to its role in angiogenesis, ANG2 promotes tumor immunosuppression through multiple mechanisms. ANG2 facilitates recruitment of immunosuppressive cells (myeloid-derived suppressor cells, regulatory T cells, and

Table 3. 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.

TIE2 [the ANG1 and ANG2 receptor] expressing monocytes) by triggering adhesion molecule expression and increasing leukocyte-endothelial interactions. In addition, ANG2 promotes immune cell migration out of the vasculature and into the tumor microenvironment. ANG2 also negatively regulates the anticancer activity of monocytes by suppressing secretion of tumor necrosis factor.[7]

Regorafenib can also directly interfere with macrophage colony-stimulating factor 1 (CSF-1) and the CSF-1 receptor axis, which promotes monocyte differentiation into tumor-associated macrophages.[7]

Preclinical Data Suggesting That Regorafenib May Sensitize Tumors to Chemotherapy

Chemosensitization is the process by which a therapeutic agent renders tumor cells more sensitive to chemotherapy, overcoming acquired chemotherapy resistance.[8] A number of preclinical studies have suggested that regorafenib may have a role in chemosensitization. The molecular mechanisms of observed synergy between regorafenib and other agents are not fully understood, but may involve the action of the proapoptotic protein PUMA and the modulation of drug transporters that can affect the concentration of chemotherapy in the tumor microenvironment.[9,10]

A study combined regorafenib with anticancer agents to test for in vitro effects on several patient-derived xenografts in mice.[11] Although regorafenib alone significantly inhibited tumor growth in several xenografts, enhanced antitumor effects were observed when regorafenib was combined with irinotecan. The authors noted that particular, chemosensitizing effects were observed with the DNA-damaging topoisomerase I inhibitor irinotecan in PDGFR-amplified tumors.

The combination of regorafenib and irinotecan inhibited the growth of oxaliplatin- and bevacizumab-refractory colon cancer tumor xenografts.[12] In this study, irinotecan alone and the regorafenib-irinotecan combination both inhibited the growth of xenografted tumors based on patient tissue samples. This combination demonstrated significant inhibition of tumor growth compared with irinotecan alone ($P<.0106$).

Regorafenib also acted synergistically with another topoisomerase inhibitor, topotecan, against colon cancer xenografts in nude mice.[13] In particular, this combination was observed to show synergistic activity in mitoxantrone-resistant xenograft tumors.

Combination treatment with regorafenib plus 5-fluorouracil also acts synergistically.[14] Regorafenib in combination with 5-fluorouracil significantly suppressed the generation of colon tumor spheres in 5-fluorouracil–resistant cells in vitro, compared with a dimethylsulfoxide (DMSO) control. Regorafenib in combination with 5-fluorouracil also significantly inhibited tumor growth in vivo, compared with the DSMO control. The study authors reported that regorafenib was associated with an increased level of the microRNA miR-34a, and that this expression may lead to the reversal of anticancer drug resistance. Another study further demonstrated synergistic activity in CRC cell lines sensitive to single-agent regorafenib and 5-fluorouracil.[15] Synergistic effects were particularly prominent in CRC cell lines that possessed *KRAS*, *BRAF*, or *P53* mutations, as well as in mismatch repair–deficient cells.

Regorafenib and the microtubule-interfering agent paclitaxel demonstrated synergistic activity against the tumor microenvironment, suppressing the growth of xenografted tumors. Importantly, these xenografts consisted of doxorubicin-resistant human colon tumors that overexpressed the membrane drug transporter ABCB1. The synergistic effects observed between regorafenib and paclitaxel were attributed to the inhibitory effect of regorafenib on ABCB1 efflux activity, which in turn facilitates paclitaxel accumulation within the tumor microenvironment.[10]

A regorafenib/cetuximab combination demonstrated synergistic activity, overcoming acquired EGFR resistance in CRC xenografts with a *KRAS* mutation and acquired cetuximab resistance. Specifically, the combination of regorafenib and cetuximab inhibited the growth of these cetuximab-resistant tumors in vivo to a greater degree than either agent alone.[16]

Clinical Data Suggesting That Regorafenib May Sensitize Tumors to Chemotherapy

The preclinical synergy observed between regorafenib and

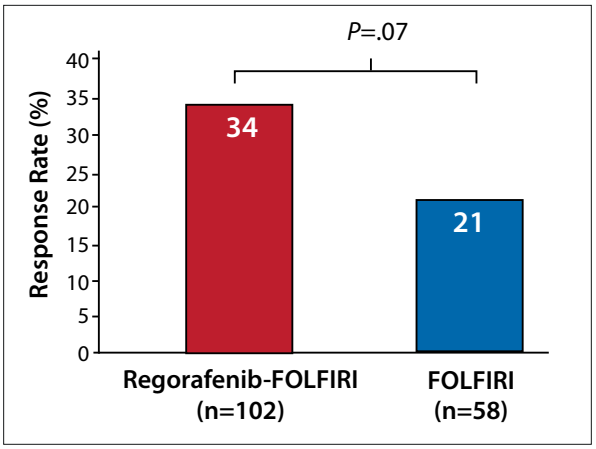

Figure 5. Response rates in a trial that evaluated sequential administration of regorafenib and FOLFIRI in patients with metastatic colorectal cancer. FOLFIRI, leucovorin, fluorouracil, and irinotecan. Adapted from Sanoff HK et al. *Cancer*. 2018;124(15):3118-3126.[19]

various agents was found to translate to the clinical setting. Collectively, these clinical studies of regorafenib and chemotherapy—administered sequentially and in combinations—resulted in increased chemotherapy exposure, improvements in survival and duration of therapy, and increases in response rates and duration of response as compared with monotherapies.

A multicenter study of regorafenib/chemotherapy combinations in 45 patients found that regorafenib increased exposure to both irinotecan and SN-38.[17] Specifically, the areas under the curve of irinotecan and SN-38 were significantly higher after regorafenib dosing compared with before.

Regorafenib administered with chemotherapy improved overall survival and PFS compared with regorafenib monotherapy in a single-center, retrospective study of 61 patients.[18] In this study, the chemotherapy agents tested in combination with regorafenib were 5-fluorouracil–based agents, namely oxaliplatin, irinotecan, FOLFOX, and FOLFIRI. Overall, the median overall survival was 20.9 months with the combination vs 10.3 months with single-agent regorafenib (*P*=.015). The median PFS was 3.7 months vs 3.5 months, respectively (*P*=.09). The median duration of therapy was 4.5 months with the combination vs 2.9 months with single-agent regorafenib (*P*=.037). Responses at 3 months were higher in the combination group vs the monotherapy group (*P*=.006). A tolerable safety profile was reported in the combination group.

Regorafenib was sequentially administered with FOLFIRI to evaluate efficacy in patients who had progressed during treatment with an oxaliplatin/fluoropyrimidine-based regimen.[19] This randomized, double-blind, placebo-controlled trial conducted across 45 academic centers included 181 patients with unresectable mCRC who had progressed on oxaliplatin and 5-fluorouracil or capecitabine (with or without prior biologic therapy). An intermittent dosing schedule of regorafenib was selected to minimize the overlap of toxicities with both treatments. Median PFS was 6.1 months with regorafenib/FOLFIRI vs 5.3 months with FOLFIRI alone (HR, 0.73; *P*=.056). The PFS in patient subgroups showed a trend toward a benefit for the sequential treatment. However, more patients in the regorafenib/FOLFIRI arm required dose reductions in 5-fluorouracil (66%) or irinotecan (66%) than patients treated with FOLFIRI alone (33% and 30%, respectively). The ORR was 34% for patients treated with regorafenib and FOLFIRI vs 21% with FOLFIRI alone, a difference that did not reach statistical significance (*P*=.07; Figure 5).[19] Median overall survival was 13.8 months vs 11.7 months, respectively, a difference that was not significant (HR, 1.01; *P*=.94). Patients treated with the sequential administration of regorafenib and FOLFIRI experienced higher rates of cytopenia than those treated with FOLFIRI alone.

The CORDIAL study (First Line Treatment of Metastatic Colorectal Cancer With mFOLFOX6 in Combination With Regorafenib) assessed the activity and tolerability of sequential administration of a modified FOLFOX regimen (mFOLFOX) and regorafenib in mCRC.[20] This international, multicenter, open-label phase 2 trial enrolled patients with mCRC eligible for treatment with mFOLFOX. mFOLFOX was administered on days 1 and 15 of a 28-day cycle, and regorafenib was administered on days 4 to 10 and 18 to 24. The investigators hypothesized that a longer duration of therapy with sequential regorafenib and FOLFOX vs standard treatment would help patients maintain tumor control. Among the primary analysis population of 41 patients, sequentially administered regorafenib and mFOLFOX6 resulted in an ORR of 43.9% and a disease control rate of 85.4%. Best change in target lesion size is shown in Figure 6. The overall duration of treatment was 9.9 months, exceeding the 6 months typically seen with standard first-line therapies in phase 3 studies. Six patients received at least 1 component of study treatment for 1 year or longer, and 5 patients were still receiving regorafenib more than 6 months after the data cutoff. Although the study did not meet its primary endpoint of an increase in response rate compared with historical controls, the observed duration of therapy led the investigators to recommend further exploration of the addition of regorafenib to standard treatment to maintain tumor control.

The REVERCE Study

REVERCE was an open-label, randomized, phase 2 Japanese trial that evaluated the sequence of regorafenib followed by cetuximab compared with cetuximab followed by

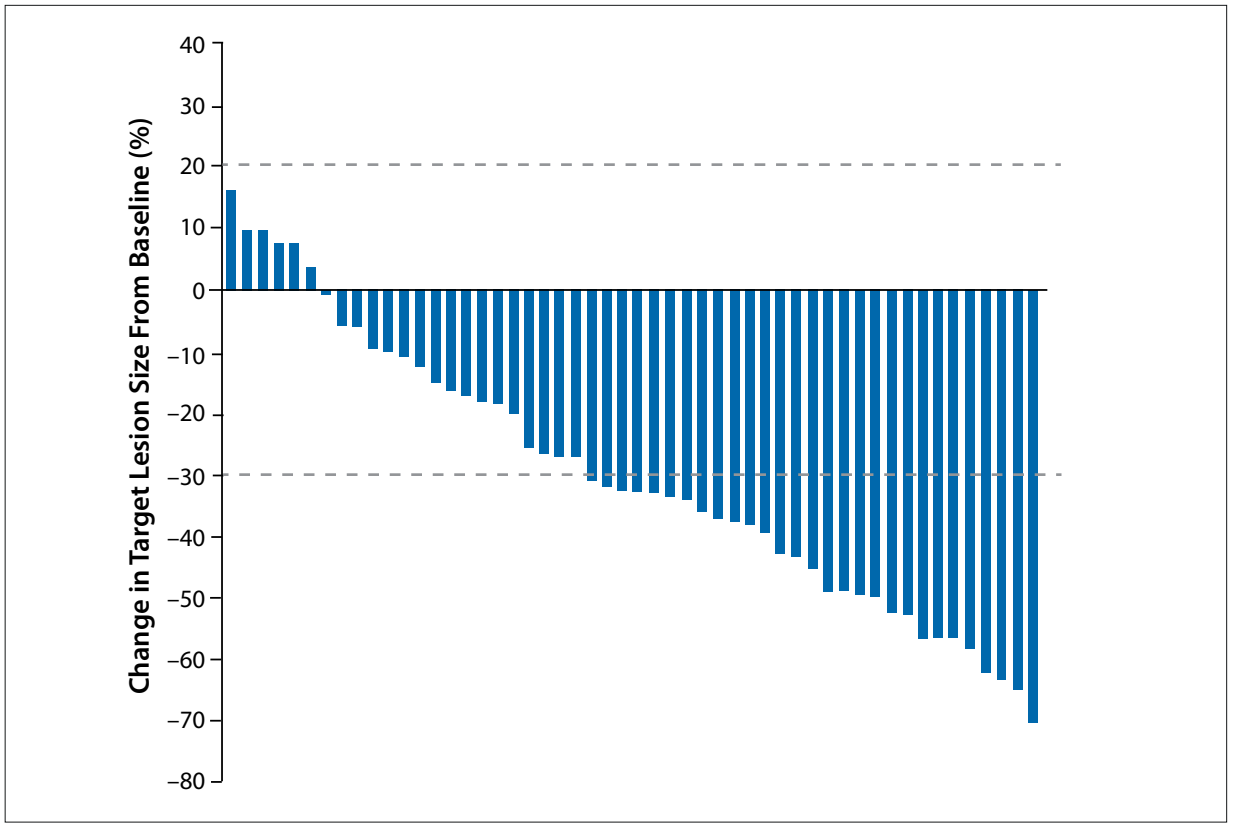

Figure 6. Best change in target lesion size in a trial of sequential administration of a modified FOLFOX regimen and regorafenib in patients with metastatic colorectal cancer. FOLFOX, leucovorin, fluorouracil, and oxaliplatin. Adapted from Argilés G et al. *Eur J Cancer*. 2015;51(8):942-949.[20]

regorafenib in patients with mCRC.[21] The study enrolled patients with confirmed locally advanced or metastatic CRC that was *KRAS* wild-type. All patients had progressed following treatment with fluoropyrimidines, oxaliplatin, and irinotecan; had an ECOG performance status of 0 to 2; and had adequate organ function.

The trial randomly assigned patients to sequential treatment with regorafenib followed by cetuximab with or without irinotecan (R-C; n=51), or sequential treatment with cetuximab with or without irinotecan followed by regorafenib (C-R; n=50). In both arms, regorafenib was administered at a dose of 160 mg once daily on days 1 to 21 of a 28-day cycle. At the time of randomization, patients were stratified by study site, prior bevacizumab treatment history, and intention to use irinotecan with cetuximab. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. In both arms, the second sequential treatment was initiated within 7 and 28 days after completion of the first treatment in the sequence, provided that all predefined criteria for treatment continuation were met.

The primary endpoint of the study was overall survival. Secondary endpoints included PFS with the initial treatment, PFS with the second treatment, safety, and quality of life. Study enrollment was stopped prematurely based on slower than expected accrual of patients and a funding shortage.

The baseline characteristics of patients were relatively similar between the study arms. The median age was 68 years in the R-C arm and 65 years in the C-R arm. In both arms, approximately two-thirds of patients were male. The primary tumor location was left-sided in 75% of patients in the R-C arm and 86% of patients in the C-R arm. Regorafenib dose reductions were required in 65% of patients in the R-C arm and 38% of patients in the C-R arm. However, the duration of regorafenib exposure was longer in the R-C arm vs the C-R arm.

Median overall survival, the primary endpoint, was 17.4 months in the R-C arm vs 11.6 months in the C-R arm (HR, 0.61; 95% CI, 0.39-0.96; stratified log-rank *P*=.0293). The median time to sequential treatment failure was also significantly prolonged with R-C vs C-R, at 7.4 months vs 6.1 months (HR, 0.60; 95% CI, 0.39-0.92; *P*=.017). Median PFS for the entire sequential therapy was 9.0 months vs 7.1 months, respectively (HR, 0.55; 95% CI, 0.34-0.90; *P*=.015).

Grade 3 or higher nonhematologic AEs reported with regorafenib occurred in 71% of the R-C arm and 63% of

the C-R arm. Those associated with cetuximab occurred in 57% of the R-C arm and 50% of the C-R arm.

Following the first treatment in the sequence, *RAS* mutations emerged in the circulating tumor DNA (ctDNA) of 1 patient following regorafenib (R-C arm) and 11 patients following cetuximab (C-R arm). Other emerging gene mutations were also identified at a greater frequency following cetuximab vs regorafenib; these events were associated with worse overall survival outcomes compared with wild-type patients.[21]

Disclosure

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How Translational Research Can Guide the Use of Regorafenib in Patients With Metastatic Colorectal Cancer

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The Impact of Regorafenib's Mechanism of Action on Treatment Sequencing

Studies conducted over the past several years have established that if patients with mCRC are treated with anti-VEGF agents in the first-line and second-line settings, then these agents should be continued in subsequent lines to improve the outcome of chemotherapy. This finding was demonstrated in a preclinical study by Mancuso and colleagues that assessed regrowth of blood vessels after VEGFR inhibition in a mouse model of lung carcinoma.[1] VEGFR inhibition led to significant loss of the tumor vasculature, which began to be repaired immediately fol-

lowing drug withdrawal and continued until the tumors were fully revascularized. Importantly, the regrown vasculature regressed to a similar degree upon re-exposure to the VEGFR inhibitor. Evidence for the importance of continuing bevacizumab was supported by clinical observations in a subgroup analysis of the phase 3 N016966 trial.[2] The analysis showed that patients who continued treatment with bevacizumab until disease progression experienced much better outcomes than those who stopped bevacizumab after 6 months.

Regorafenib blocks angiogenesis via much broader mechanisms than anti-VEGFR targeted agents, and may therefore be able to overcome resistance by targeting bypass mechanisms of anti-VEGF antibodies. Thus, there is a rationale to use regorafenib in the third-line setting if the patient had been previously exposed to an anti-VEGFR agent.

The previously described phase 3 trials CORRECT and CONCUR showed that patients treated with regorafenib have a superior prognosis when compared with placebo.[3,4] A retrospective exploratory analysis of the CORRECT trial investigated the clinical activity of regorafenib in biomarker subgroups of the patient population.[5] These subgroups were defined by tumor mutational status or plasma protein levels, which were assessed by BEAMing (beads, emulsion, amplification, magnetics) technology to identify *KRAS*, *PIK3CA*, and *BRAF* mutations in blood plasma ctDNA. Overall, this analysis showed that all patient subgroups benefited from treatment with regorafenib vs placebo. The benefit with regorafenib was maintained independent of the patient's *RAS* or *KRAS* mutation status, *PIK3CA* mutation status, or *NRAS* or *BRAF* mutation status.

Choosing Between Regorafenib and Trifluridine/Tipiracil in the Third-Line Setting

Although both regorafenib and trifluridine/tipiracil are approved for the treatment of patients with mCRC whose disease is refractory to standard chemotherapy, it remains unclear which drug should be used first. The retrospective REGOTAS study (Propensity Score Analysis of Regorafenib Versus Trifluridine/Tipiracil in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapy) addressed this question.[6] This Japanese study included 550 patients with mCRC who were treated with regorafenib (n=223) or trifluridine/tipiracil (n=327) between June 2014 and September 2015. Data were retrospectively collected from 24 institutions in Japan. Overall survival was calculated using Cox's proportional hazard models, which included a propensity score adjustment for baseline characteristics. The median overall survival among patients treated with either regorafenib or trifluridine/tipiracil was similar (7.9 vs 7.4 months, respectively). A propensity score adjusted analysis identified an adjusted HR of 0.96 (95% CI, 0.78-1.18). A statistically significant interaction with age was observed in a subgroup analysis. Regorafenib was associated with better survival in patients younger than 65 years (HR, 1.29; 95% CI, 0.98-1.69), whereas trifluridine/tipiracil was associated with better survival in patients ages 65 years and older (HR, 0.78; 95% CI, 0.59-1.03).[6]

Despite the evidence for regorafenib in the third-line setting, in clinical practice, patients are instead frequently rechallenged with an earlier treatment. However, the level of evidence supporting rechallenge is much lower than switching to third-line treatment with regorafenib,[7] which is supported by phase 3 randomized prospective clinical trials.

Sequencing Regorafenib to Optimize Timing of EGFR Inhibitor Rechallenge

The CRICKET trial (Cetuximab Rechallenge in Irinotecan-Pretreated mCRC, *KRAS*, *NRAS* and *BRAF* Wild-Type Treated in 1st Line With Anti-EGFR Therapy) evaluated the use of liquid biopsy to identify patients who might benefit from EGFR inhibitor rechallenge.[8] This small, noncomparative, prospective, open-label, multicenter, single-arm, phase 2 trial enrolled patients with *RAS/BRAF* wild-type mCRC. All 28 patients in the study were initially sensitive to first-line treatment with either FOLFOX or FOLFIRI plus cetuximab, and then developed resistance to treatment. Patients went on to second-line treatment with either FOLFOXIRI, FOLFOX, or capecitabine plus oxaliplatin, all administered with bevacizumab. Patients then received irinotecan plus cetuximab in the third-line setting.

A response was seen in 6 patients (21%); all were partial responses (Figure 7).[8] Stable disease was reported in 9 patients (32%), for a disease control rate of 54%. Among the 25 patients evaluated for a radiologic response, 52% showed tumor shrinkage. The median duration of disease control was 9.9 weeks (95% CI, 8.1-23.1). The median PFS was 3.4 months (95% CI, 1.9-3.8), and the median overall survival was 9.8 months (95% CI, 5.2-13.10).

Interestingly, *RAS* mutations were identified in liquid biopsy samples collected at the time of third-line rechallenge in 12 of 25 patients (48%) evaluated for a radiologic response with computed tomography. No *RAS* mutations were detected in the ctDNA obtained from the 4 patients whose partial response was confirmed, whereas *RAS* mutations were identified in 12 of the 21 patients (57%) who did not achieve a partial response. Median PFS was 4.0 months in patients with wild-type *RAS* vs 1.9 months in those with mutated *RAS* (HR, 0.44; 95% CI, 0.18-0.98; *P*=.03). Median overall survival was 12.5 months vs 5.2 months, respectively, but this difference was not statistically significant (HR, 0.58; 95% CI, 0.22-1.52; *P*=.24). No *BRAF* or *PIK3CA* mutations were identified

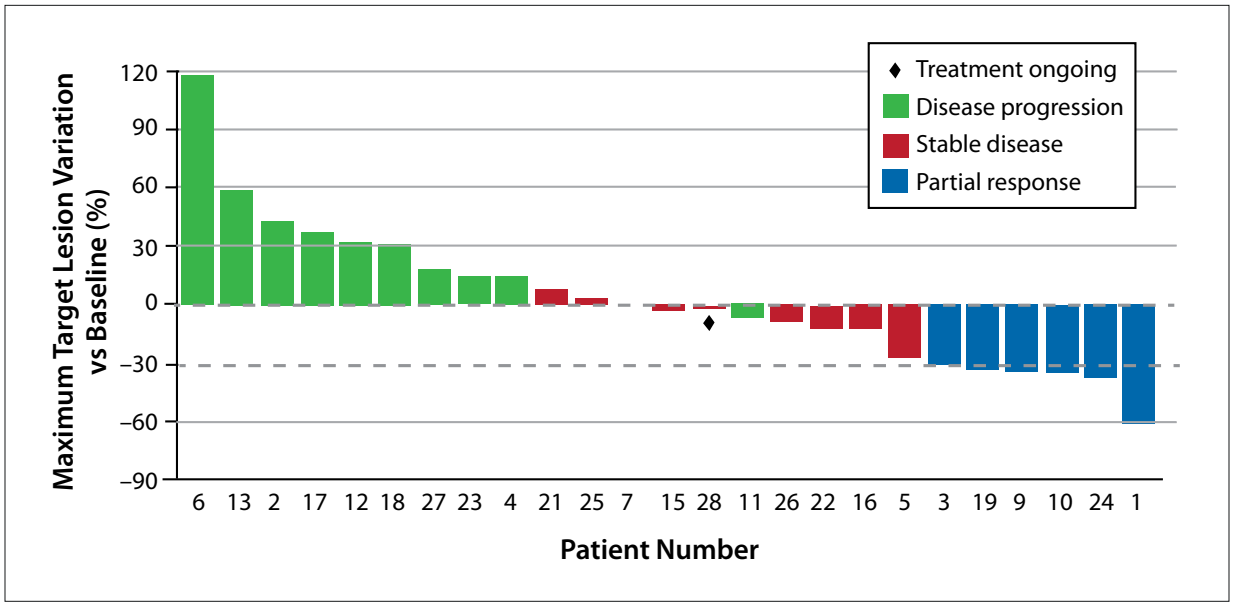

Figure 7. Tumor response in the phase 2 CRICKET trial of cetuximab rechallenge in patients with *RAS/BRAF* wild-type metastatic colorectal cancer. CRICKET, Cetuximab Rechallenge in Irinotecan-Pretreated mCRC, *KRAS*, *NRAS* and *BRAF* Wild-Type Treated in 1st line With Anti-EGFR Therapy. Adapted from Cremolini C et al. *JAMA Oncol*. 2019;5(3):343-350.[8]

Liquid biopsy represents an exciting tool to use in the future to guide physicians in selecting patients who are candidates for a rechallenge strategy. Currently, this technique is a subject of clinical trials and not a component of clinical practice.

Clones of resistance form, carrying either *RAS* or *EGFR* mutations, as a mechanism of resistance to EGFR inhibition. However, after the anti-EGFR agent is discontinued, these clones lack a growth or survival advantage compared with other tumor cells, and therefore decay. The kinetics of this decay was explored in an analysis of postprogression ctDNA profiles in 135 patients with *RAS/BRAF* wild-type mCRC who had been treated with an EGFR inhibitor and then developed either a *RAS* or *BRAF* mutation during therapy.[9] This report showed that clones with *RAS* or *EGFR* mutations decay exponentially, with a cumulative half-life of 4.4 months. These data suggest that a longer cessation of EGFR inhibitor therapy corresponds to a higher probability that rechallenge with another EGFR inhibitor will improve outcome. Thus, it is likely beneficial to wait 2 or more half-lives to increase the probability of disease control with rechallenge. One possibility is to treat with regorafenib during this wait time, to allow for a chemotherapy-free and EGFR inhibitor–free treatment regimen that is still very active. Moreover, the REVERCE study indicated that a regorafenib-cetuximab treatment sequence was associated with fewer emergent genomic alterations than a cetuximab-regorafenib sequence.[10] Patients with genomic alterations had shorter overall survival than those without such alterations (median 10 months vs 17.7 months; HR, 2.02; *P*=.027).[9]

Regorafenib in Combination With Novel Therapies

As previously described, the REVERCE trial showed that the sequence of regorafenib prior to cetuximab is superior in patients with *KRAS* wild-type mCRC.[10] One explanation for this effect, suggested by the study authors, is that regorafenib's impact on tumor mutational load is lower than that seen with anti-EGFR treatment. However, the impact of regorafenib on the antitumor immune response may offer another explanation, which is also supported by the REGONIVO study (Regorafenib and Nivolumab Simultaneous Combination Therapy).[11]

REGONIVO was a phase 1b dose-escalation trial that aimed to determine whether adding regorafenib to nivolumab could overcome nivolumab resistance mediated by tumor-associated macrophages.[11] The study consisted of a dose-finding portion, to determine dose-limiting toxicities and the maximum tolerated dose, and a dose-expansion portion, to further establish the safety and determine the preliminary efficacy of this combination. A total of 50 patients with previously treated advanced gastric cancer (n=50) or mCRC (n=50) were enrolled. Patients were heavily pretreated, with a median of 3 lines of prior therapy (range, 2-8).

Regorafenib at 80 mg to 160 mg was administered once daily for 21 days of a 28-day treatment cycle, and nivolumab at 3 mg/kg was given every 2 weeks. During the dose-escalation portion of the trial, 3 dose-limiting toxicities were observed with regorafenib 160 mg: grade 3 maculopapular rash, mucositis, and proteinuria. No dose-limiting toxicities occurred with the 80 mg or 120 mg

doses of regorafenib. In the dose-expansion cohort, the dose was reduced to 80 mg based on grade 3 skin toxicities. Grade 3 or higher treatment-related AEs occurred in 17 patients, and most frequently consisted of rash (14%), palmar-plantar erythrodysesthesia (10%), and proteinuria (8%).

The ORR was 38%, and included 7 patients with microsatellite-stable mCRC, 1 CRC patient with high microsatellite instability, and 11 patients with microsatellite-stable gastric cancer.[11] Analysis of pre- and post-treatment biopsy specimens suggested that this combination was associated with a reduction of regulatory T cells.

Disclosure

Dr Prager has attended advisory board meetings/symposiums for Merck Serono, Roche, Amgen, Sanofi, Lilly, Servier, Taiho, Bayer, BMS, Celgene, and Terumo. Dr Prager's institution has received funding for clinical trials from Celgene, Array, Servier, Bayer, Boston Biomedical, Array, Amgen, Merck, Incyte, and BMS.

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Optimizing the Treatment Sequence From Second-Line to Third-Line Therapy in Patients With Metastatic Colorectal Cancer: Discussion

Axel Grothey, MD, Gerald W. Prager, MD, Takayuki Yoshino, MD, and Tanios S. Bekaii-Saab, MD

Axel Grothey, MD What biomarkers would you like to see when evaluating the combination of regorafenib plus programmed cell death 1 (PD-1)/PD-L1 inhibitors, to increase your confidence that regorafenib works as an immunomodulator?

Gerald W. Prager, MD We are currently still learning about this issue, as the 50 patients (25 with mCRC) evaluated in the REGONIVO trial is just too few to reach any conclusions.[1] However, it will be extremely important to see a biomarker analysis of tumor biopsies, particularly of macrophages of the M2 subtype. There is preclinical evidence that anti-angiogenic agents such as regorafenib might be able to covert M2 macrophages, which are immunosuppressive, to M1 macrophages.[2,3] To my knowledge, this has not yet been studied in the REGONIVO trial. Liquid biopsy in the REGONIVO trial showed a reduction in the fraction of regulatory T cells, which was associated with response to treatment.[1]

So far, I am not convinced that there is any particular molecular subtype of mCRC that might achieve a greater benefit with the regorafenib/nivolumab regimen used in REGONIVO, except perhaps those patients with high microsatellite instability.[1] However, a good response was also observed in patients with microsatellite-stable disease.

Takayuki Yoshino, MD It is important to note that the REGONIVO trial included very selected patients with low tumor burden (including lung metastases) because some data suggested that the high tumor burden of a liver mass has a negative impact on the immune checkpoint inhibitor. However, I still believe that this combination is promising.

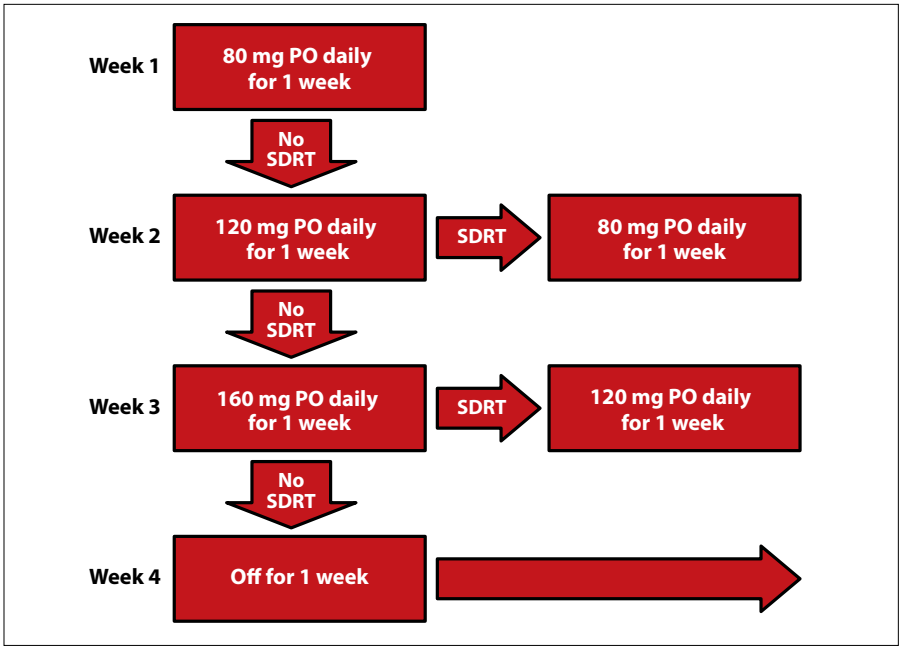

Figure 8. An incremental dose-escalation protocol for regorafenib can minimize toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol*. 2015;13(8):514-517.[8]

Axel Grothey, MD In the REGONIVO study, one of the main side effects was immune-related rash.[1] This was not the typical hand-foot skin reaction normally associated with regorafenib, but instead was a generalized rash sometimes seen with PD-1 checkpoint inhibitors. This finding suggests that we are seeing at least some activation of the immune system. Another observation is that the response rate was similar between CRC and gastric cancer. This intriguing finding suggests that this combination might be effective in other tumor types. Studies will investigate the combination of regorafenib with another PD-1 antibody, pembrolizumab, in other tumors.[4,5] Dr Bekaii-Saab, are you using the dosing strategy established in the ReDOS study (Regorafenib Dose Optimization Study) as the standard of care in your practice?

Tanios S. Bekaii-Saab, MD There had been some difficulty in using regorafenib in the clinic because the 160-mg initiation dose was tough on many patients, particularly heavily pretreated patients. The ReDOS study evaluated a dose-escalating strategy starting with a lower dose of regorafenib at 80 mg, with a goal to reach 160 mg as tolerated in patients with refractory mCRC.[6] Results from the study were incorporated into guidelines from the National Comprehensive Cancer Network.[7]

ReDOS was a randomized, multicenter, open-label, phase 2 study conducted in 39 outpatient cancer centers throughout the United States.[6] The trial enrolled patients with an ECOG performance status of 0 or 1 who had no prior exposure to regorafenib. Patients were randomly assigned to 1 of 4 treatment arms, which consisted of 2 regorafenib dosing strategies and 2 clobetasol usage plans, stratified by hospital. The standard regorafenib dosing schedule was 160 mg/day, given for 21 days of a 28-day cycle. In the dose-escalation strategy, regorafenib was started at 80 mg/day, and the dose was escalated weekly in 40-mg increments up to 160 mg/day in the absence of significant drug-related AEs (Figure 8).[8] This regimen was also given for 21 days of a 28-day cycle. Within each treatment group, patients were randomly assigned to either a preemptive or a reactive strategy for the management of hand-foot skin reaction.

The per-protocol population included 54 patients in the regorafenib dose-escalation group and 62 in the regorafenib standard-dose group. The study met its primary endpoint: the number of patients finishing cycle 2 at 8 weeks. A total of 43% of patients in the dose-escalation group initiated cycle 3 vs 26% of patients in the standard-dose group (1-sided P=.043). This primary endpoint was important for multiple reasons. It measured the likelihood that patients could tolerate treatment well enough to go beyond the second cycle. Also, it indicated that the treatment was active.

The most common grade 3/4 AEs were fatigue (13% in the dose-escalation group vs 18% in the standard-dose group), hand-foot skin reaction (15% vs 16%), abdominal pain (17% vs 6%), and hypertension (7% vs 15%). The study showed that quality of life was preserved with the dose-escalation strategy, but deteriorated with the standard dose.

Overall survival was a secondary endpoint. Median overall survival was 9.8 months in the dose-escalation group vs 6.0 months in the standard-dose group (HR, 0.72; 95% CI, 0.47-1.10; log-rank P=.12).[6] This difference was not statistically significant, but still interesting. The 6-month median overall survival was consistent with

that reported in the CORRECT and CONCUR trials, which gives us added confidence in the dose escalation strategy.[9,10]

The dose-escalation strategy used in ReDOS should now be the standard of care. It improves efficacy outcomes, the toxicity profile, and quality of life. Even considering that it was a phase 2 randomized trial, at a minimum, the ReDOS trial showed that this dose-escalation strategy is at least noninferior from an efficacy standpoint, and certainly superior in terms of safety and quality of life.

Axel Grothey, MD Dr Yoshino, are you incorporating regorafenib in sequence before cetuximab in your clinical practice, based on the REVERCE study?

Takayuki Yoshino, MD REVERCE was a randomized phase 2 study, and results must be confirmed in phase 3 studies.[11] Therefore, I have not implemented this strategy in clinical practice, and I still use regorafenib as salvage therapy. However, the REVERCE results are promising.

Gerald W. Prager, MD In our academic center, we use liquid biopsy before we rechallenge patients. This strategy is not routine throughout Austria, and it is the subject of many clinical trials. Before rechallenging in the fourth- or fifth-line, a liquid biopsy analysis can be used to confirm *RAS* mutational status. It is a quick and inexpensive test, with a short turnover time. If a liquid biopsy shows that the patient is still *RAS* wild-type, it can provide the confidence to consider rechallenge.

Axel Grothey, MD I agree. What other combination therapies do you think would be interesting for regorafenib beyond combining it with PD-1 antibodies?

Takayuki Yoshino, MD For me, the most promising combination is regorafenib plus nivolumab.

Gerald W. Prager, MD Potential combinations should reflect the toxicity profile of regorafenib as a limiting factor. It might be interesting to combine regorafenib with trifluridine/tipiracil because these treatments have completely different toxicity profiles. Currently, much research is focusing on combining regorafenib with immunotherapies. There is rationale for this strategy. There has been some success with combinations of other tyrosine kinase inhibitors with immunotherapies. It would be extremely intriguing if this concept of making a "cold" tumor "hot" can be achieved with regorafenib in mCRC. It has been seen in other tumor types. Regorafenib has activity in other diseases, such as soft tissue sarcomas and glioblastomas. The combination of regorafenib with immunotherapy might also be an option for other tumor types.

Disclosures

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