Abstract: The past decade has seen substantial improvements in outcomes among patients with metastatic colorectal cancer treated with first and second lines of therapy. An increasing number of patients are beginning third-line treatment and beyond. Patients have several options for third-line treatment. Several of these therapies are reserved for small subsets of patients with defined molecular characteristics, whereas others are available for the broader population. Regorafenib and trifluridine/tipiracil are indicated for the treatment of patients with metastatic, refractory disease. Clinical experience with these agents has generated information regarding their optimal use, particularly in minimizing and mitigating their toxicity profiles. Trials of regorafenib have evaluated alternative dosing schedules that start at a lower dose. Other approaches to optimize patient outcomes with regorafenib and trifluridine/tipiracil include the use of novel combinations with immune checkpoint inhibitors or other targeted agents. Further results of clinical trials will allow clinicians to better manage these patients, ultimately improving outcomes while maintaining quality of life.
In 2021, patients with metastatic colorectal cancer (mCRC) are achieving a median overall survival exceeding 30 months. This outcome has been reported not only in clinical trials with preselected patients, but also in real-world clinical settings. Prolonged survival (as compared with historical data) is primarily a reflection of improvements in second-line and third-line treatment options. Increasingly, more patients are fit enough to proceed to third-line treatment, which has greatly extended survival. Approximately half of patients who start first-line systemic treatment are able to initiate third-line treatment and beyond. We have seen this in Austria, as well as in other large centers worldwide. There are now questions regarding the best selection of third-line treatment options for patients.

Third-Line Treatment Options

The multikinase inhibitor regorafenib is approved by the US Food and Drug Administration (FDA) for the treatment of patients with mCRC who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti–vascular endothelial growth factor (VEGF) therapy, and, if RAS wild-type, an anti–epidermal growth factor receptor (EGFR) therapy. Another option in the third-line setting is the combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor. Trifluridine/tipiracil is also approved by the FDA for the treatment of adult patients with mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biologic therapy, and, if RAS wild-type, an anti-EGFR therapy.

Clinical Trial Data for Regorafenib

The CORRECT trial was a registrational, double-blind, placebo-controlled phase 3 trial that evaluated the use of regorafenib in patients with mCRC whose disease had progressed following treatment with all available and approved standard therapies. This international study was conducted throughout North America, Europe, Asia, and Australia. Prior therapies varied but included a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and either cetuximab or panitumumab (for patients with RAS wild-type disease). Patients were randomly assigned to treatment with regorafenib (160 mg/day for the first 3 weeks of a 4-week cycle; n=505) or placebo (n=255). All enrolled patients also received best supportive care.

Median overall survival, the primary endpoint of CORRECT, was 6.4 months with regorafenib vs 5.0 months with placebo (hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; P=.0052; Figure 1). The secondary endpoint of median progression-free survival (PFS) was 1.9 months vs 1.7 months, respectively (HR, 0.49; 95% CI, 0.42-0.58; P<.0001). Patients treated with regorafenib were more likely to achieve stable disease, which led to a higher disease control rate vs placebo (41% vs 15%, respectively; P<.0001). No complete responses were observed in either
arm, and the objective response rates were low, at 1.0% with regorafenib and 0.4% with placebo.

Adverse events led to dose modifications in 67% of the regorafenib arm vs 23% of the placebo arm.4 Adverse events most frequently occurred during the first or second treatment cycle. The most common any-grade adverse events were fatigue (47% with regorafenib vs 28% with placebo) and hand-foot skin reaction (47% vs 8%, respectively). The most common grade 3 or higher adverse events considered related to regorafenib were hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation.

The CONCUR study was subsequently conducted to confirm the efficacy and safety observed with regorafenib in the CORRECT study, as well as to broaden the population of Asian patients.4,5 These trials shared nearly identical designs. The CONCUR study confirmed the results of CORRECT. 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 2).5 The median PFS was 3.2 months vs 1.7 months, respectively (HR, 0.31; 95% CI, 0.22-0.44; 1-sided \( P < .0001 \)). All responses were partial, and occurred in 4% of the regorafenib arm and 0% of the placebo arm (1-sided \( P = .045 \)). More regorafenib-treated patients achieved stable disease, leading to a significantly higher disease control rate vs placebo (51% vs 7%, respectively; 1-sided \( P < .0001 \)). The tolerability profile of regorafenib in CONCUR was similar to that reported in CORRECT. Adverse events required treatment modifications in 71% of the regorafenib arm vs 16% of the placebo arm.

These phase 3 trials were followed by real-world studies that further supported the use of regorafenib among patients with refractory mCRC in the third-line setting.
The CONSIGN study was a prospective, open-label, single-arm phase 3b trial conducted throughout Europe, North America, Israel, and Australia. Regorafenib led to a median PFS of 2.7 months (95% CI, 2.6-2.7). Dose reductions were made in 46% of patients owing to adverse events, and 9% of patients discontinued regorafenib. The prospective, observational CORRELATE study evaluated regorafenib dosing and tolerability in an international population of patients with mCRC. Among these patients, 57% initiated regorafenib at the standard dose of 160 mg daily, 30% initiated treatment at a dose of 120 mg/day, and another 13% started at 80 mg/day or lower. Efficacy outcomes reported in CORRELATE included a median overall survival of 7.6 months (95% CI, 7.1-8.2) and a median PFS of 2.9 months (95% CI, 2.8-3.0).

A landmark analysis of a large, prospective, postmarketing Japanese surveillance study found several factors that were associated with a significant improvement in overall survival with regorafenib, including resection of the primary site, the presence of hand-foot skin reaction on day 28, and the rectum as the primary site of disease. Factors associated with reduced overall survival in this analysis included ascites, metastasis in the liver, metastasis in the bone, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, and a body surface area of less than 1.6 m². REBECCA was a prospective cohort trial embedded in an early access program in France, which found that the efficacy of regorafenib was most pronounced in patients with an ECOG performance status of 0 and 1, but less pronounced in patients with an ECOG performance status of 2 or worse.

Real-world data showed that the overall survival of patients treated with regorafenib has improved over time. This improvement can be mainly attributed to better selection of patients for treatment, as well as initiation of proactive strategies to prevent and manage adverse events.

**Clinical Trial Data for Trifluridine/Tipiracil**

Registrational data supporting the approval of trifluridine/tipiracil came from the double-blind phase 3 RECOURSE trial. This study randomly assigned 800 patients with refractory mCRC to treatment with up to 4 cycles of either trifluridine/tipiracil (35 mg/m² twice daily for 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period) or placebo. All enrolled patients were also treated with best supportive care.

Median overall survival, the primary endpoint of RECOURSE, was significantly prolonged with trifluridine/tipiracil compared with placebo (7.1 vs 5.3 months; HR, 0.68; 95% CI, 0.58-0.81; *P*<.001; Figure 3). The secondary endpoint of median PFS was also significantly longer with trifluridine/tipiracil vs placebo (2.0 vs 1.7 months; HR, 0.48; 95% CI, 0.41-0.57; *P*<.001). Objective response rates were low in both arms, and did not differ significantly between the 2 arms (1.6% with trifluridine/tipiracil vs 0.4% with placebo; *P*=.29). Stable disease was higher with trifluridine/tipiracil, accounting for a significantly better disease control rate vs placebo (44% vs 16%, respectively; *P*<.001).

Patients treated with trifluridine/tipiracil experienced a higher rate of grade 3 or higher adverse events compared with patients who received placebo. Most of these adverse events were hematologic toxicities (neutropenia [38% vs 0%], anemia [18% vs 3%], and thrombocytopenia [5% vs 0%]).
<1%) and gastrointestinal toxicities (nausea [2% vs 1%], vomiting [2% vs <1%], and diarrhea [3% vs <1%]).

The randomized, double-blind, placebo-controlled phase 3 TERRA trial was conducted to confirm the results observed with trifluridine/tipiracil in the RECURC study.11,12 Like the CONCUR trial of regorafenib, the TERRA trial sought to expand the Asian population in which trifluridine/tipiracil was tested. The TERRA trial showed that the risk of death was significantly lower with trifluridine/tipiracil vs placebo.12 The median overall survival was 7.8 vs 7.1 months, respectively (HR, 0.79; 95% CI, 0.62-0.99; log-rank P=.035). Serious adverse events were reported at similar rates in both arms.

Real-world data are also being reported with trifluridine/tipiracil. Chief among these studies is the PRE-CONNECT trial, discussed below.13

Selecting Patients to Optimize Outcomes in the Third-Line Setting and Beyond

One important strategy for improving the efficacy and safety of third-line treatment is ensuring that appropriate patients receive these therapies. Patient characteristics such as age, comorbidities, and performance status are important determinants in the first-line setting, and thus are likely to be useful gauges in the third-line setting as well.14,15 In addition, those patients with a lower tumor burden and fewer symptoms, less liver involvement, and better laboratory profiles may have a longer time to achieve a benefit from therapy.

Patients receiving either regorafenib or trifluridine/tipiracil generally have an ECOC performance status of 0 to 2. Outcomes with these agents tend to be independent of the number of prior lines of therapy, and they work well in patients with heavily pretreated disease.

Unfortunately, there are no biomarkers that can help predict which patients will benefit from these agents. However, a post hoc analysis of data from the RECURC study and the phase 2 J003 study showed that patients who develop high-grade neutropenia after trifluridine/tipiracil tend to benefit from treatment.16

Treatment Guided by Mutations

A small subgroup of patients, defined by the presence of HER2 amplification, have other treatment options after their second line of treatment. Phase 2 trials have shown that anti-HER2 drugs such as trastuzumab, lapatinib, pertuzumab, and fam-trastuzumab deruxtecan-nxki are effective in patients with RAS wild-type disease who are also positive for HER2 amplification.17-19 Another small subgroup of patients who have a high degree of microsatellite instability (MSI-high) and/or are deficient in mismatch repair pathway proteins (dMMR) are able to receive treatment with the immune checkpoint inhibitors nivolumab, pembrolizumab, or dostarlimab-gxly (if not received during earlier lines of therapy).20-23 Unfortunately, both of these subgroups account for only a small minority of patients initiating third-line treatment: approximately 3% in the case of patients with a HER2 amplification, and approximately 5% to 10% of those with MSI-high/dMMR disease.

For patients who have RAS wild-type disease and who have received anti-EGFR antibodies, another alternative third-line option is rechallenge with an anti-EGFR agent. For example, the CRICKET trial was prospectively designed to investigate a rechallenge strategy with irinotecan and cetuximab as third-line therapy among patients who experienced an initial response and then progressed during treatment with a first-line irinotecan- and cetuximab-containing therapy, and then received chemotherapy plus bevacizumab in the second-line setting.24 Importantly, this study incorporated translational analysis of circulating tumor DNA (ctDNA) via liquid biopsy. Patients who benefitted from this rechallenge strategy were more likely to have RAS wild-type status according to ctDNA analysis. These data were exciting, but the overall level of evidence was low. However, this strategy remains an alternative for consideration in the appropriate patient population.

Disclosure

Dr Prager has attended advisory board meetings/symposia for Merck Serono, BMS, Roche, Amgen, Lilly, Servier, Taiho, Bayer, Halozyme, MSD, Celgene, Incyte, and Pierre Fabre.

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Measures to Mitigate Treatment-Related Toxicities in Third-Line Metastatic Colorectal Cancer

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Regorafenib and trifluridine/tipiracil have proven efficacy as third-line treatments in patients with mCRC. However, their use can be limited by issues related to tolerability. Toxicity is of particular concern in patients with refractory mCRC, who have already received multiple chemotherapeutic and targeted agents and often have experienced multiple related side effects, some of which can be long-term. These patients may also be facing a deteriorating performance status owing to these prior toxicities as well as progressive disease. Therefore, treatment options for this setting must offer tumor stabilization without significant toxicity, to allow prolonged duration of therapy. The balance between toxicity and efficacy is crucial throughout the management of patients with mCRC, but is perhaps never more important than when the patient enters the third line of treatment.

Mitigation of Toxicities Related to Regorafenib

The toxicities associated with regorafenib are not typically life-threatening. However, they can result in a significant negative impact on the patient’s quality of life. Some of the more common adverse events include hand-foot skin reaction, diarrhea, fatigue, and asthenia. In the registrational phase 3 CORRECT study, hand-foot skin reaction of any grade occurred in 47% of regorafenib-treated patients, which included grade 3 events in 17% and no grade 4 events. Diarrhea of any grade occurred in 34%,
including grade 3 in 7% and grade 4 in less than 1%. Any-grade fatigue was reported in 47% of patients in the regorafenib arm; these cases were grade 3 in 9% and grade 4 in less than 1%.

In clinical practice, it is often necessary to provide recommendations and prescriptions for dermatologic creams to prevent hand-foot skin reaction. Although these creams do not always completely prevent hand-foot skin reaction, they can mitigate the severity. Loperamide is a typical treatment for diarrhea that may ameliorate this reaction.

As described in the regorafenib prescribing information, it is sometimes necessary to modify the dosing strategy. Interruption of regorafenib is recommended in cases of grade 2 hand-foot skin reaction that is recurrent or does not improve within 7 days despite dose reduction (interrupt therapy for a minimum of 7 days for grade 3 events). Other situations in which regorafenib interruption is recommended include symptomatic grade 2 hypertension, any grade 3 or 4 adverse reaction, and worsening infection of any grade. Dose reduction of regorafenib to 120 mg is recommended at the first occurrence of grade 2 hand-foot skin reaction that is recurrent, following recovery of any grade 3 or 4 adverse reaction except infection, and for grade 3 elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT); in this latter event, regorafenib should be resumed only if the potential benefit outweighs the risk of hepatotoxicity. Further dose reduction to 80 mg is recommended when grade 2 hand-foot skin reaction recurs at the 120-mg dose, and after recovery of any grade 3 or 4 adverse reaction at the 120-mg dose (except hepatotoxicity or infection). According to the prescribing information, regorafenib should be discontinued in patients who are unable to tolerate the 80-mg dose, and those with any occurrence of AST or ALT elevation more than 20 times the upper limit of normal (ULN), any occurrence of AST or ALT more than 3 times the ULN with concurrent bilirubin more than 2 times the ULN, re-occurrence of AST or ALT more than 5 times the ULN despite a dose reduction to 120 mg, and for any grade 4 adverse reaction.

**Regorafenib Dose-Escalation Strategy**

The toxicities associated with regorafenib often require either dose reductions or treatment interruptions, which can prevent the patient from reaching the maximal clinical activity of treatment. As a result, dose reduction strategies, as pioneered in the practice-changing ReDOS trial, have been examined as a means to mitigate these toxicities.

The ReDOS trial was a randomized phase 2 study that postulated that mitigating or reducing the regorafenib dosing regimen would decrease the associated toxicities and in turn allow patients to prolong their duration of regorafenib treatment. Patients were randomly assigned to either a standard dosing schedule of regorafenib (the approved dose of 160 mg once daily) or a dose-escalated schedule in which regorafenib was initiated at 80 mg/day during the first week, increased to 120 mg/day during week 2, and then increased to the standard dose of 160 mg/day during week 3 (Figure 4). In this dose-escalated
arm, patients were evaluated weekly to determine if their toxicity burden would allow their dose to be increased. While patients in the standard-dosing arm continued the same dose in cycle 2 and beyond, patients in the dose-escalated schedule arm initiated cycle 2 with a regorafenib dose that was determined by the maximal dose that was tolerated during the first cycle. In both treatment arms, regorafenib was administered on a 3-weeks-on and 1-week-off cycle.

The primary endpoint of the ReDOS trial was the proportion of patients who completed 2 cycles of therapy and initiated the third cycle.4 Twice as many patients in the dose-escalated arm achieved this endpoint as compared with the standard-dose arm (43% vs 26%; 1-sided P=.043). The median overall survival was slightly prolonged in the dose-escalated arm compared with the standard-dose arm, although this difference was not statistically significant (9.8 vs 6.0 months, respectively; HR, 0.72; 95% CI, 0.47-1.10; log-rank P=.12; Figure 5).

During cycles 1 and 2, patients treated with the dose-escalated strategy experienced fewer grade 3 adverse events commonly associated with regorafenib, including fatigue, hand-foot skin reaction (Table 1), hypertension, and diarrhea.4 In the dose-escalated vs standard-dose arms, the most frequent grade 3 or 4 adverse events reported were fatigue (13% vs 18%), hand-foot skin reaction (15% vs 16%), abdominal pain (17% vs 6%), and hypertension (7% vs 15%). The cumulative dose of regorafenib was relatively similar between the 2 arms, which suggested that the overall regorafenib exposure during cycles 1 and 2 was important. Fewer dose modifications were required in the dose-escalated group (22%) vs the standard-dose group (32%). Further, no dose delays were required in the dose-escalation arm, while 7 patients (15%) required a delay of regorafenib in the standard-dose arm.

The authors of the ReDOS study concluded that the dose-escalation strategy for regorafenib administration was an appropriate and effective method to optimize the duration and exposure of regorafenib while achieving a lower incidence of adverse events.4

A preplanned analysis of the ReDOS study evaluated the preemptive vs reactive use of clobetasol 0.05% corticosteroid cream as a means to mitigate hand-foot skin reaction associated with regorafenib.5 This analysis was confined to the first 2 cycles of regorafenib in ReDOS. The study demonstrated that preemptive application of clobetasol cream may better reduce hand-foot skin reactions. During the first 2 regorafenib cycles, no evidence of hand-foot skin reactions was reported in 30% of patients treated with preemptive clobetasol vs 13% of patients treated with reactive clobetasol (P=.03). During cycle 2, the incidence of hand-foot skin reaction was 30% (grade 1), 8% (grade 2), and 3% (grade 3) in preemptively treated patients, vs 43%, 18%, and 7%, respectively, in reactively treated patients (P=.12). Importantly, patients treated reactively reported worse quality of life owing to hand-foot skin reactions.

Mitigation of Toxicities Related to Trifluridine/Tipiracil

The primary side effects of trifluridine/tipiracil are hematologic toxicities, most typically neutropenia and anemia (but rarely febrile neutropenia). With some exceptions,
these toxicities do not typically have a negative impact on the patient’s quality of life; however, they can be very serious. For example, a patient who develops a grade 4 neutropenia has a high risk of severe and potentially life-threatening infection. In the registrational RECOURSE phase 3 study, any-grade hematologic toxicities were frequent in the trifluridine/tipiracil arm and included neutropenia in 67% (grade ≥3 in 38%), leukopenia in 77% (grade ≥3 in 21%), anemia in 77% (grade ≥3 in 18%), and thrombocytopenia in 42% (grade ≥3 in 5%).

Gastrointestinal toxicities are another common side effect associated with trifluridine/tipiracil, and can be disturbing to patients. Any-grade gastrointestinal-related toxicities reported in the RECOURSE study included nausea in 48% (grade ≥3 in 2%), vomiting in 28% (grade ≥3 in 2%), decreased appetite in 39% (grade ≥3 in 4%), diarrhea in 32% (grade ≥3 in 3%), and abdominal pain in 21% (grade ≥3 in 2%).

Somewhat paradoxically, colorectal oncologists may find the hematologic toxicities and gastrointestinal toxicities resulting from trifluridine/tipiracil reasonably manageable, as they are similar to those seen with classical chemotherapy regimens that these clinicians have a great deal of experience with. In clinical practice, gastrointestinal toxicities are typically managed with dose interruption of the trifluridine/tipiracil. However, mitigation of the hematologic toxicities is not as well established. Among patients who develop a severe neutropenia, hematologic growth factors are often used to try to prevent further worsening of the neutropenia. However, the optimal time to administer these growth factors is unknown.

The trifluridine/tipiracil prescribing information recommends that clinicians obtain complete blood cell counts prior to and on day 15 of each treatment cycle. Treatment should not be initiated unless and until the absolute neutrophil count (ANC) is at least 1,500/mm³, any febrile neutropenia is resolved, platelets are 75,000/mm³ or higher, and grade 3 or 4 nonhematologic adverse reactions are resolved to grade 1 or less. During the treatment cycle, trifluridine/tipiracil should be withheld in cases of ANC less than 500/mm³, febrile neutropenia, platelets below 50,000/mm³, or a grade 3 or 4 nonhematologic adverse reaction. After recovery, the recommendation is to resume trifluridine/tipiracil with a dose reduction of 5 mg/m² from the previous dose, if the following occur: febrile neutropenia; uncomplicated grade 4 neutropenia (which has recovered to ≥1,500/mm³) or thrombocytopenia (which has recovered to ≥75,000/mm³) that results in a delay of more than 1 week in the start of the next cycle; or a nonhematologic grade 3 or 4 adverse reaction (except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or grade 3 diarrhea responsive to antidiarrheal medication). A maximum of 3 dose reductions are permitted. Trifluridine/tipiracil should be permanently discontinued in patients who are unable to tolerate a dose of 20 mg/m² orally twice daily.

The PRECONNECT Trial of Trifluridine/Tipiracil

The PRECONNECT study is an international, multicenter, open-label phase 3b trial conducted to provide a
large population of eligible patients with mCRC early access to trifluridine/tipiracil. In addition to assessing the safety and efficacy of trifluridine/tipiracil in these patients, patient-reported outcomes were also evaluated. A total of 917 patients were enrolled in the study. At baseline, most patients had an ECOG performance status of either 0 (48.7%) or 1 (48.0%), and 52.6% had a RAS mutation. The median age was 62 years (range 24-87), and 59.9% were male. Left colonic disease was common (62.5%), as was liver metastases (72.6%). Most patients (63.4%) were treated with 3 or more prior lines of therapy.

Overall, the efficacy results reported in the PRECONNECT trial were similar to those observed in the RECOURSE trial. The median PFS among trifluridine/tipiracil-treated patients was 2.8 months (95% CI, 2.7-2.9). An objective response occurred in 18 (2.3%) patients. The disease control rate, which included stable disease, was 34.4%.

The median time to deterioration in performance status (an ECOG score of ≥2) was 8.9 months (range, 0.03-14.7). This duration was longer among patients who had previously received 2 lines or fewer of therapy compared with patients who had received more than 2 lines of therapy (14.3 vs 8.5 months, respectively).

The safety results from the PRECONNECT trial were similar to those reported in the RECOURSE trial. The most common drug-related treatment-emergent adverse events reported in this population of patients were neutropenia (51.7%), asthenia/fatigue (27.0%), nausea (26.6%), anemia (20.6%), and diarrhea (20.2%). The most frequent grade 3 or higher drug-related treatment-emergent adverse events were neutropenia (38.2%), anemia (6.5%), asthenia/fatigue (3.2%), and diarrhea (3.2%).

After 7 treatment cycles, the mean changes from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Global Health Status (EORTC QLQ-C30 GHS) score quality of life measure were not clinically relevant at any time point. The mean score was 56.2±23.8 at baseline and 58.3 (interquartile range [IQR], 25.0) at the time of study withdrawal. The EORTC QLQ-C30 GHS score improved from baseline to end of treatment in 20.4% of patients, improved or did not deteriorate in 55.9% of patients, and deteriorated from baseline to end of treatment in 44.1% of patients. A deterioration in the patients’ ECOG performance status was noted at a median duration of 8.9 months (Figure 6).

**Sequencing Treatment Approaches in the Third-Line and Beyond**

One of the most pressing questions in the management of patients with refractory mCRC is the optimal sequence of therapies in the third-line setting and beyond. The ongoing randomized phase 2 SOREGATT study is evaluating the best sequence of administration of regorafenib and trifluridine/tipiracil, with the goal of optimizing overall survival while maintaining quality of life. In SOREGATT, regorafenib is administered using the dose-escalation schedule established in ReDOS. Trifluridine/tipiracil is administered at a dose of 35 mg/m² twice daily on days 1 to 5 and days 8 to 12 of each 4-week cycle. The primary endpoint of the trial is the treatment feasibility of
the 2 sequences (regorafenib followed by trifluridine/tipiracil as compared with trifluridine/tipiracil followed by regorafenib). Treatment feasibility will be measured as the percentage of patients able to receive at least 2 cycles of both treatments. Secondary endpoints are overall survival, PFS, disease control rate, objective response rate, time to treatment failure, time to ECOG performance status deterioration to 2 or higher, quality of life, and safety.

Disclosure
Dr Ducreux has received honoraria from Servier, Lilly, Amgen, Roche/Genentech, Merck Serono, MSD Oncology, Ipsen, Bayer, Celgene, and Novartis. He has a consulting or an advisory role at Roche, Merck Serono, Servier, Amgen, Novartis, Ipsen, Celgene, Lilly, Pierre Fabre, and HalioDx. He is a member of the speakers' bureaus of Roche, Merck KGaA, Celgene, Ipsen, and Bayer. He has received research funding from Roche and Keocyt. He has received reimbursement for travel, accommodations, and expenses from Ipsen, Roche, Merck Serono, Bayer, and Amgen. His wife is head of the Oncology Business Unit of the French affiliate of Sandoz.

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Recent Study Data in Third-Line Metastatic Colorectal Cancer
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Chemorefractory mCRC is one of the primary challenges in the field of medical oncology, particularly because colorectal cancer remains one of the leading cancer diagnoses worldwide. According to the World Health Organization, in 2020, colorectal cancer was the third most frequently diagnosed cancer and the second-leading cause of cancer-related deaths (Figure 7).

Fortunately, the treatment regimens available for both the first-line and second-line mCRC settings provide good clinical benefit in terms of tumor response, as well as prolongation of PFS. Overall survival has increased owing to a combination of treatment benefits in the first-line, second-line, and third-line settings. More than half of patients with mCRC enter the third-line treatment setting. Many of these patients enter the third line reasonably fit and with a good performance status, and thus it is necessary to provide them with good therapeutic options. Historically, oncologists have not had good treatment options in this setting and were limited to attempting a rechallenge with a combination chemotherapy regimen that the patient had already received in an earlier stage of the disease.

This approach changed several years ago with the regulatory approvals of 2 novel therapeutic options for the third-line treatment of mCRC: regorafenib and trifluridine/tipiracil. Although both treatment options demonstrated a survival benefit in phase 3 trials, their clinical efficacy appears to be lower than that achieved.
with first-line and second-line regimens. These agents are associated with different safety profiles. Regorafenib exhibits side effects that are in line with other multikinase inhibitors; they include fatigue, hypertension, hand-foot syndrome, and loss of appetite. The side effects associated with trifluridine/tipiracil resemble those of chemotherapy, and include hematologic toxicities, gastrointestinal adverse events, and fatigue. Therefore, some of the most pressing unmet needs involve improving the clinical efficacy as well as the safety profiles of both agents. The ReDOS study was an important step, and provided a new dose-escalation approach for treating patients with regorafenib. Other prospective trials have also been conducted to further improve the efficacy and safety of both third-line treatment options.

The REARRANGE Trial of Regorafenib Dosing Strategies

The REARRANGE trial is the largest prospective trial designed to evaluate how different initial dosing strategies for regorafenib might impact the tolerability profile. REARRANGE was a phase 2 study conducted in Spain, Italy, and France that randomly assigned 299 patients across 3 regorafenib treatment arms. The 3 arms differed in the administration of regorafenib during cycle 1, then used the same approved dosing regimen (continuous 4-week cycles of 160 mg/day of regorafenib for 3 weeks on followed by 1 week off) for cycle 2 and beyond. Arm A (the control arm) administered regorafenib at the approved dosing regimen. Arm B (dose-reduced schedule) was one type of dose-reduction strategy. During cycle 1, regorafenib was administered at 120 mg/day for 3 weeks followed by 1 week off for the first cycle. Arm C (intermittent schedule) was a second type of dose-reduction strategy. During cycle 1, regorafenib was administered at 160 mg/day for weeks 1 and 3 and held for weeks 2 and 4 of cycle 1. In all 3 arms, patients were treated until disease progression or intolerable toxicity.

The primary endpoint of the REARRANGE trial was safety, assessed as the percentage of patients who experienced a grade 3 or 4 adverse event during the entire treatment course. Secondary endpoints included overall survival, PFS, the percentage of patients able to initiate cycle 3, dose intensity, and the disease control rate. Patient characteristics were evenly distributed across the 3 treatment arms. The median age ranged from 63 to 65 years, with a minority of patients (18% to 21%) older than 70 years. The population had a slight male preponderance (53% to 58%). RAS mutations were present in 61% to 71% of patients, and BRAF mutations were present in 2% to 3%. Most patients had liver metastases (74% to 78%), and many patients had 3 or more sites of metastases (43% to 53%). Left-sided disease was predominant (68% to 80%), as was prior primary tumor resection (80% to 82%). Patients were relatively heavily pretreated, with a mean of 3.9 to 4.1 prior lines of therapy.

Analysis of the primary endpoint showed that there was no statistically significant improvement in the tolerability of regorafenib in either of the experimental...
arms compared with the control arm. A total of 60% of patients in the control arm experienced a grade 3/4 adverse event during the treatment course, compared with 54% with the dose-reduced schedule in arm B ($P=0.4730$) and 55% with the intermittent schedule in arm C ($P=0.5673$). Further, neither experimental arm reached the threshold to achieve positivity in the primary endpoint of safety compared with the control arm.

Interestingly, there were some hints of improvement in tolerability with the experimental dosing strategies. For example, more patients in arm B (43%) and arm C (45%) were able to initiate cycle 3 of regorafenib compared with arm A (39%), although this difference did not reach statistical significance ($P=0.4730$). Further, the incidence of some grade 3/4 adverse events during the entire treatment course was numerically less in the experimental arms vs the control arm. Grade 3/4 asthenia/fatigue occurred in 20% of patients in arm A, compared with 14% and 15% of patients in arms B and C, respectively. Grade 3/4 hypertension occurred in 19% of patients in arm A, which was higher than in arm B (12%) but similar to arm C (20%). Grade 3/4 hand-foot skin reaction occurred with an incidence of 8% in arm A, 7% in arm B, and 3% in arm C.

Importantly, there appeared to be no effect on efficacy between the experimental and control arms ($P=0.7152$). Median overall survival was 7.4 months in the control arm, compared with 8.6 months with the dose-reduced schedule in arm B and 7.1 months with the intermittent schedule in arm C. Similarly, there was not a significant difference in median PFS across the treatment arms (1.9 months in arm A, compared with 2.0 months in arm B and 2.0 months in arm C; $P=0.3871$).

Together these results led the REARRANGE study investigators to conclude that while neither experimental regorafenib dosing strategy resulted in a statistically significant improvement in the general tolerability profiles, the alternative schedules are of reasonable consideration given the improvements seen in those adverse events considered to be of importance by patients and physicians. These improvements did not come at the expense of efficacy, as shown by the overlapping intervals for PFS and overall survival in the 3 arms. When these results are considered in the context of the findings from the ReDOS trial, they reinforce the idea that initiating regorafenib with a more flexible and lower dose before gradually increasing it in the absence of toxicity may help more patients to continue therapy and allow them more time to experience benefit from the drug.

### Regorafenib Plus Nivolumab

The single-arm phase 1b REGONIVO study in Japan sought to determine if the addition of the programmed death 1 receptor (PD-1)-targeted immune checkpoint inhibitor nivolumab could augment the clinical activity of regorafenib in patients with mCRC (n=25) or gastric cancer (n=25). Among patients with mCRC, the objective response rate was 36% and the median PFS was 7.9 months, which appear to be superior to results achieved with either drug alone in the same setting in which trifluridine/tipiracil or regorafenib are used. PFS in patients with colorectal cancer according to programmed death ligand 1 combined positive score is shown in Figure 8.
The authors of the REGONIVO study noted that all but 1 of the 9 objective responses occurred in patients with microsatellite-stable (MSS)/mismatch repair–proficient (pMMR) mCRC, which is notably resistant to PD-1 checkpoint blockade.10,11 These promising data caused a great deal of excitement in the field, and led to the development of an open-label phase 2 North American study in the same population, but restricted just to MSS/pMMR patients.12 All 70 patients enrolled in this single-arm study received regorafenib (initiated at 80 mg/day and dose-escalated to 120 mg/day on a schedule of 3 weeks on followed by 1 week off) plus nivolumab (administered at a dosage of 480 mg every 4 weeks).12 Patients were relatively young, with a median age of 57 years (range, 34-85). A total of 47% of patients had left-sided disease, while 36% had right-sided disease. In 17%, the primary site of disease was localized to the rectum. The majority of patients (93%) had a tumor histology of adenocarcinoma, not otherwise specified. Liver (67%) and lung (73%) metastases were common. Almost two-thirds (61%) of patients had a \( \text{KRAS} \) or \( \text{NRAS} \) mutation, and 4% had a \( \text{BRAF} \) mutation. More than half of the patients had received 3 or more prior lines of therapy.

The primary endpoint of the study was the investigator-assessed objective response rate, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. No complete responses were reported, while 5 patients (all without liver metastases) achieved a partial response.12 The objective response rate was 7%. When just the 23 patients without liver metastases were considered, the objective response rate was 22%. In both cases, these response rates were far lower than the initial results reported in the REGONIVO trial, and were viewed by the scientific community as more reflective of reality.

The median overall survival in the entire study population was 11.9 months (95% CI, 7.0 months to not evaluable).12 Survival did not seem to be affected by the extent of liver metastases, as the median overall survival was 11.0 months (95% CI, 7.9-11.9) in patients without liver metastases and 10.7 months (95% CI, 6.1 months to not evaluable) in patients with liver metastases.

Patients were unable to receive treatment for a prolonged duration. The median duration of treatment was 2.2 months (range, 0.7-11.7) for regorafenib and 1.9 months (range, 0.03-11.1) for nivolumab.12 Grade 3 treatment-emergent adverse events that were considered to be drug-related occurred in 40% of patients, and 3% developed grade 4 events. The most common grade 3/4 treatment-emergent, treatment-related adverse events were maculopapular rash in 14% (all grade 3), fatigue in 7% (all grade 3), pneumonia in 5% (4% grade 3; 1% grade 4), and increases in blood levels of bilirubin in 6% (3% grade 3; 3% grade 4). Two patients developed a grade 5 adverse event. Treatment-emergent adverse events considered to be related to the drug required a dose interruption of regorafenib in 46% of patients and of nivolumab in 11% of patients.

The analysis of the final data set from this study will be crucial to draw conclusions regarding which patients should be selected for further evaluation of this combination. In particular, the final analysis should provide insight into whether there is a subgroup of patients likely to achieve long-term benefit—in light of the objective safety profile—that warrants further exploration of this combination in a phase 3 trial.

**Trifluridine/Tipiracil Plus Nivolumab**

The combination of trifluridine/tipiracil plus nivolumab was evaluated in a single-arm phase 2 trial in patients with MSS mCRC that was refractory to standard treatment regimens.13 Patients were treated with trifluridine/tipiracil at a dosage of 35 mg/m² twice daily on days 1 to 5 and 8 to 12 of a 28-day cycle and with nivolumab at a dosage of 3 mg/kg on days 1 and 15 of each 28-day cycle. A total of 18 patients were enrolled into the first stage of the study. Among these 18 patients, 50% were male and the median age was 56.5 years. About half of the patients (56%) had a \( \text{KRAS} \) mutation.

No objective responses were observed among the 18 patients enrolled. Ten patients (56%) achieved a best overall response of stable disease per RECIST criteria, and the median PFS was 2.8 months.

Grade 3 or higher adverse events owing to any cause occurred in 72% of patients, and consisted most frequently of neutropenia (28%), diarrhea (17%), and abdominal pain, anemia, fatigue, and nausea (11% each).13 Grade 3 or higher adverse events that were considered related to a study drug occurred in 56% (trifluridine/tipiracil) and 28% (nivolumab) of patients. No grade 5 adverse events occurred. Dose modifications were required for trifluridine/tipiracil in 61% of patients and for nivolumab in 17% of patients.

After this interim analysis, the study was stopped based on lack of efficacy. No further patients were enrolled. At the time of data cutoff, all patients had experienced disease progression and had discontinued treatment. The study authors concluded that the addition of nivolumab to trifluridine/tipiracil failed to improve the efficacy of the latter agent in this MSS mCRC patient population.13

**Trifluridine/Tipiracil Plus Bevacizumab**

An open-label phase 2 Danish study reported promising results with the addition of the antiangiogenic agent...
bevacizumab to trifluridine/tipiracil in 93 patients with chemorefractory mCRC. Prior exposure to bevacizumab, aflibercept, ramucirumab, or regorafenib was permitted. This study randomly assigned patients to treatment with either trifluridine/tipiracil alone (at a dosage of 35 mg/m² twice daily on days 1 to 5 and 8 to 12 every 28 days) or the same dosage of trifluridine/tipiracil plus bevacizumab (5 mg/kg on days 1 and 15). Treatment was continued until disease progression or unacceptable toxicity.

Across the treatment arms, the median patient age was 65 years (IQR, 57-72). In the trifluridine/tipiracil-alone arm, 64% of patients were male, 77% had left-sided disease, and 62% had a RAS mutation. In the trifluridine/tipiracil-plus-bevacizumab arm, 52% of patients were male, 76% had left-sided disease, and 59% had a RAS mutation. Patients were heavily pretreated across the 2 treatment arms; 57% and 54% had received 3 or more prior lines of therapy, respectively.

The primary endpoint, investigator-assessed PFS, was significantly prolonged with the addition of bevacizumab to trifluridine/tipiracil as compared with trifluridine/tipiracil alone (median PFS, 4.6 vs 2.6 months; HR, 0.45; 95% CI, 0.29-0.72; P=0.0010). This difference remained significant even when adjusted for stratification factors (eg, RAS mutation status and institution). Median overall survival, a secondary endpoint, was also significantly prolonged with the combination (9.4 vs 6.7 months; HR, 0.55; 95% CI, 0.32-0.95; P=0.028). One patient in the trifluridine/tipiracil-plus-bevacizumab arm experienced a partial response, while no responses occurred in the trifluridine/tipiracil-alone arm.

Neutropenia was the most common grade 3 or higher adverse event in both arms, and was higher with the addition of bevacizumab (38% with trifluridine/tipiracil alone and 67% with trifluridine/tipiracil plus bevacizumab). No deaths from treatment-related adverse events were reported.

The results from this investigator-initiated phase 2 trial seem very promising, with a doubling of the PFS with the combination compared with trifluridine/tipiracil alone in the context of the safety profile presented in the experimental arm. These data led to the initiation of the open-label, multinational phase 3 SUNLIGHT trial, which is evaluating treatment in the third-line setting for patients with unresectable mCRC. An estimated 490 patients will be enrolled and randomly assigned to treatment with the current standard of care (trifluridine/tipiracil alone) or the addition of bevacizumab to trifluridine/tipiracil. The primary endpoint is overall survival.

Disclosure
Dr Argilés has a compensated advisory role for Gadeta BV and Agen.

References
Optimizing Administration of Third-Line Treatment in Metastatic Colorectal Cancer: Q&A

Gerald W. Prager, MD, and Guillem Argilés, MD

Gerald Prager, MD What is your perspective from your experience in the United States regarding third-line treatment options? Did you experience differences between US colleagues and European colleagues in prescribing one or the other drug?

Guillem Argilés, MD There are many differences, as you can imagine, in the treatment of refractory mCRC between Europe and America. Usually, in the United States, clinicians tend to make more decisions based on phase 2 studies in this setting, mainly owing to the differences in therapy recommendation requirements between guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology. For example, the ReDOS strategy is often used during treatment with regorafenib. However, clinicians often do not exactly follow the strategy in the trial. Instead of starting the dose at 80 mg, many clinicians start at 120 mg, then manage from there. There is also more use of trifluridine/tipiracil plus bevacizumab based on the promising phase 2 study. Notably, this regimen is recommended in the NCCN guidelines, even in the absence of data from a phase 3 trial. In the United States, pembrolizumab is also available to treat the small subset of patients with colorectal cancer who have a high tumor mutational burden. Anti–PD-1 agents, however, are not available in Europe for the MSS population. Overall, there are more treatment options available in the United States than in Europe.

Gerald Prager, MD Can you also discuss the choice to rechallenge patients? Do you perform a ctDNA assessment via liquid biopsy prior to proceeding with anti-EGFR in the third-line rechallenge setting? Or is this approach relegated to clinical trials?

Guillem Argilés, MD The majority of oncologists still base rechallenging decisions on clinical information. Several groups provided data to define a well-established clinical criteria for rechallenge. Thus, the vast majority of medical oncologists are making decisions based on these clinical criteria, given difficulties in accessing ctDNA tests, turnover times, and lack of standardization among platforms. In large and more specialized centers, where there is greater access to liquid biopsy, rechallenge is beginning to be implemented more frequently.

In Europe, for RAS wild-type patients with left-sided disease, treatment tends to start with an anti-EGFR agent in the first line as the preferred option, and then shifts toward an anti-VEGF agent in the second-line setting. As a result, there is more room for rechallenge in either the third-line or perhaps the fourth-line settings. In contrast, in the United States, anti-EGFR therapies are often reserved for the refractory setting owing to rash and other associated toxicities that may occur. As a result, the room for rechallenge is lower because not all patients can arrive at a hypothetical fifth line of treatment, even now. As a result, fewer patients overall are rechallenged with EGFR-targeted agents in the United States as compared with Europe.

Gerald Prager, MD I can also discuss treatment in Europe. I recently had a discussion about the dose-escalation strategy for regorafenib with my European colleagues. It was very interesting to see that approximately two-thirds of my European colleagues are using the dose-escalation design. Most of my colleagues are aware of the concept of dose escalation in the first cycle, although only a few know the exact data of the ReDOS study. Some clinicians in China are using a 120 mg/day flat dose, which is not escalated. This strategy is derived from their own real-world data. This approach is not followed in Europe, and thus, I support the dose-escalation concept. However, it is an interesting approach. The toxicity profile might differ a little in the Chinese patient population.

Guillem Argilés, MD The final outcomes from the REARRANGE trial should help to illuminate application of the dose-escalation strategy to the European setting. The setting matters. I do not see easy implementation of the ReDOS strategy in Europe, where patient follow-up generally requires a greater workload for the physician as compared with the United States. Therefore, the weekly assessment of patients required with the ReDOS strategy is very challenging for the majority of practices in Europe.

Results from the REARRANGE trial, which was performed in a European environment, are currently being submitted for publication. We demonstrated an improvement in the figures for the most worrisome adverse events associated with regorafenib in each of the 2 dose-reduced
arms. Once the study results are published, there will be a clearer path for a dose-reduction strategy for the European setting.

**Gerald Prager, MD** Yes, I agree. Let me ask you about the future. You were mentioning the trial combining trifluridine/tipiracil with bevacizumab, which is already included in the NCCN guidelines (suggesting that it will get reimbursed by European health care systems). The worldwide phase 3 SUNLIGHT trial is studying this concept. Positive results might lead to the approval or extension of the label in Europe. What is your perspective on this combination? In addition, trials of regorafenib in combination with checkpoint inhibitors are providing somewhat controversial but promising data. Where do you see regorafenib in the future?

**Guillem Argilés, MD** The combination of trifluridine/tipiracil plus bevacizumab is interesting and perhaps holds the strongest position among the candidate combinations to become the next standard of care for refractory mCRC. The phase 2 study showed an increase in efficacy without a significant increase in adverse events. The adverse event profile of trifluridine/tipiracil plus bevacizumab is similar to that associated with other drugs used in our daily practice, and it is therefore likely that clinicians will feel comfortable with this combination.

Regorafenib combinations appear to be leaning toward immunotherapy, which might prove to be more complicated, as these combinations will be associated with a unique immune-related adverse event profile. Although we are gaining more experience in managing regorafenib-related adverse events, oncologists who treat colorectal cancer are not frequent prescribers of immunotherapy. Thus, there will be a learning curve in this area.

In terms of the future for regorafenib, I think it is quite interesting that there is a group of patients who seem to do particularly well with regorafenib, enjoying prolonged benefits that were observed throughout both the registrational and postmarketing studies. The future may revolve around biomarkers that will allow identification of patients who can achieve a long-term benefit. Further research may also explore regorafenib-based combinations (perhaps with immunotherapy) in patients with low tumor involvement in the always-elusive liver, who could perhaps derive a greater benefit.

**Gerald Prager, MD** Do you see a role for either of these drugs as maintenance treatment or in earlier lines of therapy?

**Guillem Argilés, MD** Yes, I think that maintenance after first-line induction is a promising scenario to continue increasing overall survival in mCRC in the short term. There have been several trials exploring regorafenib as maintenance, including one in Italy. I think there is potentially a role here, for example, in patients who have achieved a partial response given the broad antiangiogenic mechanism of action of regorafenib. We published a trial combining FOLFFOX plus regorafenib in first-line therapy, and the safety was very favorable. However, there are several other options in the maintenance setting with favorable results, and it is still difficult at this point to predict which one may become the most beneficial.

**References**

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**Third-Line Treatment of mCRC**
- The treatment regimens available for both the first-line and second-line mCRC settings provide clinical benefits in terms of tumor response and survival outcomes.1-3
- More than half of patients with mCRC enter the third-line treatment setting.
- Many of these patients enter the third-line setting reasonably fit and with a good performance status.

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**Third-Line Treatment Options for mCRC**
- Regorafenib
  - A multikinase inhibitor
- Trifluridine/tipiracil
  - A nucleoside metabolic inhibitor plus a thymidine phosphorylase inhibitor

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**Treatment for Patients With Mutations**
- Anti-HER2 drugs such as trastuzumab, lapatinib, pertuzumab, and fam-trastuzumab deruxtecan-nadox are effective in patients with RAS wild-type disease who are also positive for HER2 amplification.4
- Patients who are MSI-high and/or dMMR can receive the immune checkpoint inhibitors nivolumab, pembrolizumab, or durvalumab-gzly (if not received during earlier lines of therapy).
- For patients who have RAS wild-type disease and who have received anti-EGFR antibodies, another option is rechallenge with an anti-EGFR agent.

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**Selecting Patients to Optimize Outcomes in the Third-Line Setting and Beyond**
- It is important to ensure that appropriate patients receive these therapies.
- Age, comorbidities, and performance status are important determinants in the first-line setting, and thus are likely to be useful gauges in the third-line setting.2
- Patients with a lower tumor burden and fewer symptoms, less liver involvement, and better laboratory profiles may have a longer time to achieve a benefit from therapy.
- Patients receiving either regorafenib or trifluridine/tipiracil generally have an ECOG performance status of 0 to 2.
- These agents work well in patients with heavily pretreated disease.

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**Toxicity in Patients With mCRC**
- Toxicity is of particular concern in patients with refractory mCRC, who have already received multiple chemotherapy and targeted agents and often have experienced multiple related side effects, some of which can be long-term.
- These patients may also be facing a deteriorating performance status owing to these prior toxicities as well as progressive disease.
- Treatment options in this setting must offer tumor stabilization without significant toxicity, to allow prolonged duration of therapy. The balance between toxicity and efficacy is crucial throughout the management of patients with mCRC, but is perhaps never more important than when the patient enters the third line of treatment.

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**Toxicities Associated With Third-Line Treatments**
- The toxicities associated with regorafenib are not typically life-threatening. However, they can negatively impact the patient’s quality of life. Some of the more common adverse events include hand-foot skin reaction, diarrhea, fatigue, and asthenia.
- The primary side effects related to trifluridine/tipiracil are hematologic toxicities, most typically neutropenia and anemia (but rarely febrile neutropenia). With some exceptions, these toxicities do not typically have a negative impact on the patients’ quality of life. However, they can be very serious.
Mitigation of Toxicities Related to Regorafenib

- In clinical practice, it is often necessary to provide prescriptions for dermatologic creams to prevent hand-foot skin reaction. Loperamide is a typical treatment for diarrhea.
- The phase 2 ReDOS study showed that a dose-escalation strategy was an effective method to optimize the duration and exposure of regorafenib while achieving a lower incidence of adverse events.
- Patients were randomly assigned to either the standard dose of 160 mg once daily or a dose-escalated schedule in which regorafenib was initiated at 80 mg/day during the first week, increased to 120 mg/day during week 2, and increased to 160 mg/day during week 3.

The REARRANGE Trial of Regorafenib Dosing Strategies

- The phase 3 REARRANGE trial evaluated 3 dosing strategies. The 3 arms differed in the administration of regorafenib during cycle 1, then used the same approved dosing regimen.
- Arm A (the control arm): Regorafenib at the approved dosing regimen.
- Arm B (dose-reduced schedule): During cycle 1, regorafenib was administered at 120 mg/day for 3 weeks followed by 1 week off for the first cycle.
- Arm C (intermittent schedule): During cycle 1, regorafenib was administered at the 160 mg/day dose for weeks 1 and 3 and held for weeks 2 and 4 of cycle 1.
- In all 3 arms, patients were treated until disease progression or intolerable toxicity.

The REARRANGE Trial: Results

- Analysis of the primary endpoint showed no statistically significant improvement in the tolerability of regorafenib in either of the experimental arms vs the control arm.
- A grade 3/4 adverse event was reported in 60% of arm A, 54% of arm B (P = 0.030), and 55% of arm C (P = 0.573).
- Neither experimental arm reached the threshold to achieve positivity in the primary endpoint of safety compared with the control arm.
- There were some hints of improvement in tolerability with the experimental dosing strategies.
- There appeared to be no effect on efficacy between the experimental and control arms.
- These results led the study investigators to conclude that while neither experimental regorafenib dosing strategy resulted in a statistically significant improvement in the general tolerability profiles, the alternative schedules are of reasonable consideration given the improvements seen in these adverse events considered to be of importance by patients and physicians.

Mitigation of Toxicities Related to Trifluridine/Tipiracil

- Gastrointestinal toxicities are typically managed with dose interruption.
- Among patients who develop severe neutropenia, hematologic growth factors are often used to try to prevent further worsening of this event. However, the optimal time to administer these growth factors is unknown.
- Dose reductions are needed in patients who develop low absolute neutrophil counts.

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