Abstract: In 2012, the US Food and Drug Administration approved the kinase inhibitor regorafenib for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti–vascular endothelial growth factor therapy; and, if RAS wild-type, an anti–epidermal growth factor receptor therapy. This approval brought a much-needed noncytotoxic chemotherapy treatment alternative to this heavily pretreated patient population. Initial phase 3 randomized clinical trials established an overall survival benefit associated with regorafenib, an important outcome addressing an unmet need for these patients. Despite these clinical data, it remains unclear exactly how regorafenib exerts its clinical activity. Preclinical data have attributed multiple mechanisms of action to regorafenib; however, which of these are important to the clinical effects of regorafenib remains unclear. This insight into the multiple mechanisms of action of regorafenib in metastatic colorectal cancer has provided the basis for new clinical trials investigating novel combinations of this therapy.
Regorafenib has emerged as a treatment option for patients with metastatic colorectal cancer (mCRC) previously exposed to 2 rounds of chemotherapy, supporting the notion that the more treatment options that patients have extending into multiple lines of therapy, the longer their overall survival. The US Food and Drug Administration (FDA) approved regorafenib 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.1

A Multipronged Mechanism of Action

An understanding of regorafenib’s mechanism of action can provide insight into how this treatment benefits patients and prolongs overall survival in mCRC. It is first important to realize that regorafenib is not a traditional cytotoxic chemotherapy. Instead, it is a multi-targeted therapy, with a unique mechanism of action that inhibits various aspects of tumor biology and tumor-host interaction (Table 1). Regorafenib is a small molecule that inhibits multiple membrane-bound and intracellular kinases involved in normal cellular functions and pathologic processes, such as tumor angiogenesis, metastasis, oncogenesis, and tumor immunity. This in itself is an important concept: regorafenib acts in a 4-pronged approach against multiple tumors pathways.

Table 1. Regorafenib: Mechanisms of Action

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

As an anti-angiogenesis agent, regorafenib inhibits the VEGF receptors (VEGFs) 1, 2, and 3. Inhibition of angiogenesis has an established benefit in the treatment of mCRC, and multiple agents with this activity are approved
in this setting. For example, the anti-VEGF antibody bevacizumab (in combination with chemotherapy) is used for the treatment of mCRC in both the first-line and second-line settings. Ramucirumab is a VEGFR2 antagonist approved in combination with chemotherapy for the treatment of patients with mCRC that has progressed during or after treatment with bevacizumab plus chemotherapy. Ziv-aflibercept acts as a soluble receptor that binds to VEGF-A and is approved in combination with chemotherapy to treat patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen.

Regorafenib also acts beyond inhibition of VEGFR to inhibit angiogenesis, including via inhibition of fibroblast growth factor receptors (FGFR) 1 and 2, the angioptin-1 receptor TIE2, and platelet-derived growth factor receptors (PDGFRs) α and β. Importantly, each of these targets have different roles in tumor angiogenesis. The VEGF pathway is important for the formation of new blood vessels. FGFR1/2 and TIE2 help form precursors in the bone marrow (bone marrow–derived stem cells) that are necessary for blood cell formation. PDGFRα/β promotes the growth of blood vessels.

Both FGFR and PDGFR have emerged as potential mechanisms of resistance in tumors that begin to show proliferation despite anti-VEGF pathway inhibition. This finding suggests that regorafenib can target the VEGFR pathway to attenuate angiogenesis, while limiting the tumor’s secondary resistance mechanisms via inhibition of FGFR and PDGFR. In this way, inhibition of angiogenesis—an effective target in mCRC—can continue to be a goal beyond disease progression. Indeed, this may be one of the explanations for why a survival benefit is observed with regorafenib.

**Metastasis**

A second mechanism of action attributed to regorafenib is inhibition of tumor metastasis, which is thought to occur through both antiangiogenic and antiproliferative mechanisms. For example, inhibition of VEGFR2-mediated signaling by regorafenib induces a reduction of microvessels and increases apoptosis. Inhibition of VEGFR3 may help reduce metastatic spread by blocking tumor lymphangiogenesis and preventing endothelial sprouting and vascular network formation.

**Oncogenesis**

Another way regorafenib acts is as an oncogenesis inhibitor. Regorafenib blocks multiple oncogenic pathways, including RAF-1, which is part of the mitogen-activated protein kinase (MAPK) pathway; RET; and KIT. Inhibition of these signal transduction pathways in cancer cells can inhibit cell proliferation and survival signaling, and increase proapoptotic signaling pathways.

**Figure 1.** In a highly aggressive murine CT26 metastatic colon cancer model, regorafenib significantly decreased F4/80+ macrophages on day 14 postimplantation. Adapted from Abou-Elkacem L et al. *Mol Cancer Ther*. 2013;12(7):1322-1331.

**Tumor Immunity**

A novel fourth mechanism of action has recently been attributed to regorafenib. This drug appears to show immunomodulatory properties. The immune system is known to interact with tumors, targeting cancer cells for destruction. Regorafenib is thought to participate in this antitumor immune response in different ways. Regorafenib inhibits CSF1R, a tyrosine kinase receptor that is involved in macrophage proliferation. Macrophages are generally thought to be part of the immunostimulatory response, but macrophages can in fact both stimulate and inhibit the immune response. During the anticancer immune response, macrophages play a negative role in terms of antitumor immunity, meaning they can dampen the immune response mounted against cancer cells. Thus, inhibition of the CSF1R may reduce the recruitment of tumor-associated macrophages (TAMs) to the tumor bed, limiting their function. Regorafenib was shown to reduce macrophage infiltration in a highly aggressive murine CT26 metastatic colon cancer model (Figure 1). The ability of regorafenib to modulate anti-tumor immune suppression has been a focus in recent years, particularly with the rise of immune checkpoint inhibitor therapy. It is hypothesized that regorafenib may work in concert with anti–programmed cell death 1 (PD-1) and anti–programmed cell death ligand 1 (PD-L1) antibodies to augment the anticancer immune response. Inhibitors of the PD-1/PD-L1 immune checkpoint (such as nivolumab, pembrolizumab, and atezolizumab) have become important therapeutic agents against multiple solid tumors. Early data from the phase 1 REGONIVO
study (Regorafenib and Nivolumab Simultaneous Combination Therapy; discussed in greater detail later in this monograph) suggest that combining regorafenib with the anti–PD-1 therapy nivolumab resulted in a robust decrease in the number of regulatory T cells (Tregs) within the population of tumor-infiltrating lymphocytes.10

Importance of Regorafenib’s Diverse Mechanism of Action to the Cancer Patient

Intriguingly, despite knowledge of regorafenib’s cellular targets, it remains unclear which of these mechanisms of action is most responsible for the efficacy seen in individual patients. It is possible that regorafenib works differently in different patients, and/or that the activity is drawn from its varied factors working in concert. These factors could differ from patient to patient and from disease to disease, as regorafenib has demonstrated activity in a diverse group of cancers in addition to mCRC, including hepatocellular carcinoma, gastric cancer, sarcomas, gastrointestinal stromal tumors, and even glioblastomas. Thus, the large spectrum of anticancer activity across different tumor types is probably related to the fact that regorafenib inhibits very different components of tumor biology.

How to best utilize these different mechanisms of action in patients is an interesting question. By the time patients have progressed to third-line treatment, they have received a great deal of chemotherapy. Many of these patients may have exhausted their bone marrow reserve, and they may show signs of neutropenia and thrombocytopenia. Therefore, having a nonmyelotoxic option by the third-line setting or later may be an attractive alternative to allow time for bone marrow recovery. In this case, regorafenib offers the additional benefit of exposing the cancer cells to a very different mechanism of action, which may then have implications for anti-tumor efficacy. When patients require subsequent treatment after regorafenib, evidence suggests that chemotherapy is active.11

Discussing Regorafenib as a Treatment Option With Patients

When describing the mechanism of action of regorafenib to patients, I begin by saying that they are getting a break from chemotherapy. By switching to regorafenib, the aim is to target the tumor in a very different way, by trying to hit the biologic points that are critical for tumor cell survival and proliferation. There is uncertainty regarding regorafenib’s exact mechanism of action. However, the abundance of clinical data show that carefully selected patients (primarily defined by a good performance status) benefit from the use of this unique agent.

Disclosure

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

References

The multipronged mechanism of action of regorafenib likely explains its observed activity in the later-line setting of mCRC, among heavily pretreated patients. This activity was established in two phase 3 randomized clinical trials. Since their publication, several postmarketing and real-world clinical studies have further confirmed this activity, while suggesting a potential increase in benefit when regorafenib is used in earlier lines of therapy. In addition, clinical studies have focused on the use of regorafenib in novel combinations and sequences.

The CORRECT Trial

The CORRECT trial (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) was a randomized, placebo-controlled phase 3 study that enrolled patients from 16 countries throughout North America, Europe, Asia, and Australia. Patients were randomly assigned in a 2:1 fashion to treatment with either regorafenib (160 mg once daily for the first 3 weeks of each 4-week cycle) or placebo. Dose modifications were permitted to mitigate adverse effects. Treatment was continued until disease progression or unacceptable toxicity. All patients also received best supportive care.

A total of 760 patients received treatment in the CORRECT trial between April 2010 and March 2011. The trial enrolled adult patients with confirmed mCRC who developed disease progression after receiving all approved standard therapies. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 3 months; and adequate bone marrow, liver, and renal function.

Baseline characteristics were widely similar between the regorafenib and placebo arms, with a few exceptions. In both arms, the patients’ median age was 61 years, and 61% were male. At baseline, patients had an ECOG performance status of either 0 (54%) or 1 (46%). The colon was the most frequent primary site of disease (65%), and adenocarcinoma was the most common tumor histology (97%). A BRAF mutation was seen in 3.3%. The median time from diagnosis of metastasis to study enrollment was 31.0 months in the regorafenib arm and 29.9 months in the placebo arm. Nearly half of enrolled patients (48%) had received 4 or more prior systemic therapies prior to the study.

The median duration of treatment was 1.7 months (interquartile range [IQR], 1.4-3.7) in the regorafenib arm and 1.6 months (IQR, 1.3-1.7) in the placebo arm. Dose modifications were required by 76% of patients in the regorafenib arm vs 38% of patients in the placebo arm. The most frequent reason for dose modification was an adverse event, most commonly dermatologic, gastrointestinal, constitutional, and metabolic or laboratory events.

The primary endpoint of the CORRECT study, overall survival, was met. At the second planned interim analysis, the median overall survival was 6.4 months (IQR, 3.6-11.8) in the regorafenib arm and 5.0 months (IQR, 2.8-10.4) in the placebo arm (hazard ratio [HR], 0.77; 95% CI, 0.64-0.94; P=.0052; Figure 2).1 The benefit in overall survival with regorafenib was observed in nearly all patient subgroups analyzed, with the exception of those with primary disease in the colon and rectum. Compared with placebo, the beneficial effect on survival associated with regorafenib was larger in the subgroup of patients with colon cancer (HR, 0.70; 95% CI, 0.56-0.89) than among patients with rectal cancer (HR, 0.95; 95% CI, 0.63-1.43).

The secondary endpoint of progression-free survival (PFS) was a median of 1.9 months with regorafenib vs 1.7 months with placebo, a difference that was statistically significant (HR, 0.49; 95% CI, 0.42-0.58; P<.0001).1 Unlike with overall survival, the beneficial effect with regorafenib on PFS was similar in patients with colon vs
rectal cancer. All subgroup analyses for PFS significantly favored regorafenib, with the exception of patients from eastern Europe (who showed no difference in PFS with treatment).

Other secondary efficacy endpoints of the CORRECT study included the rates of objective response and disease control. The objective response rate was 1.0% with regorafenib and 0.4% with placebo, a difference that was not significant ($P=0.19$). No patients in the study had a complete response. The rate of disease control (which included patients with a response or stable disease) was significantly higher with regorafenib, at 41%, vs 15% with placebo ($P<0.0001$). The median duration of stable disease was 2.0 months (IQR, 1.7-4.0) with regorafenib compared with 1.7 months (IQR, 1.4-1.9) with placebo.

In the regorafenib arm, the most frequently reported any-grade adverse events were fatigue (47% vs 28% with placebo) and hand-foot skin reaction (47% vs 8% with placebo). Most patients who experienced an adverse event did so early in the course of treatment, usually during the first 2 cycles. The incidence of grade 3 or 4 treatment-related adverse events was increased with regorafenib (54%) vs placebo (14%). The most common grade 3 or higher adverse events in the regorafenib arm were hand-foot skin reaction (17% vs <1% in the placebo arm), fatigue (10% vs 5%), diarrhea (7% vs 1%), hypertension (7% vs 1%), and rash or desquamation (6% vs 0%).

The authors of the CORRECT study concluded that the addition of regorafenib to best supportive care provided a benefit in overall survival in patients with mCRC who developed disease progression after treatment with all of the standard-of-care options. The authors noted that although the improvement in median overall survival was modest, at 1.4 months, the HR indicated that regorafenib was associated with a 23% reduction in the risk of death among this population of patients with an extremely poor prognosis.

**The CONCUR Trial**

The CORRECT trial demonstrated a significant benefit in overall survival with the addition of regorafenib to best supportive care. However, the study enrolled a low proportion of patients who were Asian. For new drugs, it is important to confirm efficacy and toxicity profiles in both non-Asian and Asian populations, as some agents have shown important differences between the 2 groups. Among the 760 patients treated in the CORRECT trial, just 15% were Asian, and of these, 90% were Japanese.

Therefore, the investigators of the CONCUR trial (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) sought to evaluate regorafenib in a broader population of Asian patients.

The CONCUR trial was similar in design to the CORRECT trial. Both were randomized, double-blind, placebo-controlled phase 3 trials. The CONCUR trial enrolled patients from throughout Asia, including
mainland China, Hong Kong, South Korea, Taiwan, and Vietnam. Patients were randomly assigned in a 2:1 fashion to receive either regorafenib (160 mg once daily for the first 3 weeks of each 4-week cycle) or placebo, both added to best supportive care. Patients continued treatment until disease progression or unacceptable toxicity, and dose modifications were permitted to mitigate adverse events.

The CONCUR trial treated 204 patients between April 2012 and January 2013.1,2 The eligibility criteria for the CONCUR trial were similar to those of the CORRECT trial: histologically confirmed mCRC with disease progression. The CONCUR trial enrolled patients who had received at least 2 prior lines of treatment, including a fluoropyrimidine plus oxaliplatin or irinotecan. In contrast to the CORRECT trial, previous treatment with bevacizumab, cetuximab, or panitumumab was allowed, but not required. All patients had an ECOG performance status of 0 or 1, life expectancy of at least 3 months, and adequate bone marrow, liver, and renal function.

Overall, baseline characteristics were well balanced between the regorafenib and placebo arms. The patients' median age was 57.5 years in the regorafenib arm and 55.5 years in the placebo arm. Most patients (58%) were male. Patients had an ECOG performance status of either 0 (25%) or 1 (75%). The colon was the primary site of disease in 58% of the regorafenib arm and 71% of the placebo arm. Nearly all patients (96%) had adenocarcinoma histology. The frequency of the KRAS mutation was 31%, and just 1 patient had a BRAF mutation. A total of 40% of patients had not previously received any targeted biologic treatment, and 53% had received 4 or more lines of treatment for mCRC.

The median duration of treatment was 2.4 months (IQR, 1.6-5.3) with regorafenib and 1.6 months for placebo (IQR, 1.1-1.6). Dose modifications were required for 75% of the regorafenib-treated patients and 22% of the placebo-treated patients. Adverse events led to discontinuation of the study drug in 14% of the regorafenib arm and 6% of the placebo arm. The most common adverse events leading to discontinuation were laboratory events. Adverse events led to treatment modifications in 71% of the regorafenib arm and 16% of the placebo arm; the most frequent of these were hand-foot skin reaction and laboratory events.

The primary endpoint of the CONCUR trial, overall survival, was 8.8 months with regorafenib and 6.3 months with placebo, a significant difference (HR, 0.55; 95% CI, 0.40-0.77; \( P = .00016 \); Figure 3). The secondary endpoint of PFS was significantly improved with regorafenib. The median PFS was 3.2 months with regorafenib vs 1.7 months with placebo (HR, 0.31; 95% CI, 0.22-0.44; \( P < .0001 \)).

The benefits associated with regorafenib for both overall survival and PFS were consistent across most subgroups. An exploratory analysis found that the HR for survival was 0.31 (95% CI, 0.19-0.53) in favor of regorafenib among the 82 patients without prior treatment
with a biologic agent, and 0.78 (95% CI, 0.51-1.19) among the 122 patients who had received prior treatment with at least 1 biologic agent.

The objective response rate, another secondary endpoint, was 4% among regorafenib-treated patients (all partial responses) and 0% among placebo-treated patients ($P=.045$). Among the 6 patients with a partial response, the median duration of response was 4.8 months (IQR, 3.8-14.4). The rate of disease control (patients with either a response or stable disease) was significantly higher in the regorafenib arm compared with the placebo arm (51% vs 7%; $P<.0001$).

The rate of grade 3 or higher drug-related adverse events was 54% among patients treated with regorafenib vs 15% among patients treated with placebo. The most frequent grade 3 or higher drug-related adverse events in the regorafenib arm were hand-foot skin reaction (16%), hypertension (11%), hyperbilirubinemia (7%), hypophosphatemia (7%), alanine aminotransferase concentration increase (7%), and aspartate aminotransferase concentration increase (6%).

The CONCUR study investigators concluded that the benefit of regorafenib on overall survival in an Asian population was consistent with the improvement demonstrated in the primarily non-Asian population of the CORRECT study.$^2$ CONCUR was the second phase 3 trial to show an overall survival benefit with the addition of regorafenib to best supportive care in patients with mCRC who progressed on standard therapy. The authors noted that the HR for overall survival in CONCUR (0.55) was seemingly of greater magnitude than the benefit shown in CORRECT (0.77).$^1,2$ Although cross-trial comparisons cannot be made, the CONCUR investigators suggested that this improvement could be attributed to the lower proportion of patients in CONCUR who had prior exposure to a biologic agent (60%) compared with the CORRECT trial (100%).

The CONSIGN Study

The CONSIGN study (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy) aimed to assess the safety of regorafenib in a much larger patient population, and to better estimate PFS with regorafenib.$^3$ This prospective, open-label, single-arm phase 3b study was conducted throughout Europe, North America, Israel, and Australia.

Eligibility criteria for the CONSIGN study included a confirmed diagnosis of adenocarcinoma of the colon or rectum with disease progression, an ECOG performance status of 0 or 1, and prior treatment with approved standard therapies, including a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab/panitumumab (for patients with KRAS wild-type tumors).

The CONSIGN study enrolled 2872 patients from April 2012 to December 2013.$^3$ The median age of the population was 62 years, and 59% were male. Patients had an ECOG performance status of 0 (47%) or 1 (53%). The primary site of disease in most cases was the colon (64%), and 77% of patients had liver metastases at baseline. Approximately 51% of patients had a KRAS mutation, and 1% had a verified BRAF mutation. Patients had a varied treatment background, with 17 (1%) treated with regorafenib as a first-line therapy. The number of prior treatment regimens was 1 in 4%, 2 in 22%, 3 in 27%, and 4 or more in 46%. Nearly all patients (96%) had received previous treatment with bevacizumab.

All patients received regorafenib at 160 mg once daily for 3 weeks on and 1 week off of a 4-week cycle, administered until disease progression or unacceptable toxicity.$^1$ Dose modifications were permitted as necessary. Unlike the CORRECT and CONCUR trials,$^1,2$ in which the primary endpoint was overall survival, the primary endpoint of the CONSIGN trial was safety. The only efficacy variable analyzed as an endpoint was PFS. The median duration of regorafenib treatment was 2.5 months (range, 0.03-30.4).

The frequency of treatment-emergent adverse events was highest during the first 2 cycles of regorafenib. The most commonly reported grade 3 or higher regorafenib-related treatment-emergent adverse events were hypertension (15%), hand-foot skin reaction (14%), fatigue (13%), diarrhea (5%), and hypophosphatemia (5%). A total of 44% of patients developed a serious treatment-emergent adverse event, and 9% of these events were related to regorafenib. Grade 3 or 4 treatment-emergent laboratory abnormalities included increased bilirubin (13%), increased aspartate aminotransferase (AST; 7%), and increased alanine transaminase (ALT; 6%).

Treatment-emergent adverse events led to treatment discontinuation in 25% of patients (9% of events were related to regorafenib). The most common treatment-emergent adverse events that led to treatment discontinuation, regardless of whether they were considered related to regorafenib, were general disorders and administrative site conditions/other (reported in 6%; most frequently, general physical health deterioration, fatigue (3%), and increased bilirubin (2%). Hand-foot skin reaction required discontinuation of treatment in 1% of patients. Treatment-emergent adverse events led to treatment interruption or delay in 68% of patients and to dose reduction in 46% of patients. The most frequent treatment-emergent adverse events leading to dose reduction were hand-foot skin reaction (17%), fatigue (9%), diarrhea (5%), and hypertension (4%).
Regorafenib-related grade 3 or higher treatment-emergent adverse events occurred at a slightly higher frequency in older patients, at 64% in patients ages 75 years and older, 59% in those ages 65 to 74 years, and 55% in those younger than 65 years.

The median PFS was 2.7 months (95% CI, 2.6-2.7). Explanatory analyses demonstrated longer PFS durations among those patients with better performance status, no liver metastases, and a longer time since diagnosis of metastatic disease.

The authors of the CONSIGN study concluded that these data, obtained from a very large patient population, were consistent with the results from the randomized phase 3 studies of regorafenib, with a similar duration of median PFS and a comparable toxicity profile.3

The REBECCA Study

The REBECCA trial (Regorafenib in Metastatic Colorectal Cancer: a French Compassionate Program) was a cohort study designed to evaluate the efficacy and safety of regorafenib in a real-world clinical setting. This study, conducted at multiple institutions throughout France, included 654 patients with mCRC who had previously received standard treatment or were not considered candidates for it. All patients were treated with regorafenib from October 2012 to January 2014.

At baseline, the median age of patients was 64 years. Patients had an ECOG performance status of 0 (31%), 1 (59%), 2 (9%), or 3 (1%). The colon was the site of disease in 70% of patients, and 66% of patients had synchronous metastases. Approximately 53% of patients had a KRAS mutation. A total of 35% of patients had received at least 3 prior lines of treatment for metastatic disease; 15% had received 5 lines or more. Nearly all patients (99%) had received prior oxaliplatin and irinotecan, 92% had received prior bevacizumab, and 97% of patients with KRAS wild-type tumors had received prior anti-EGFR therapy.

The median duration of regorafenib therapy was 2.2 months (range, 0.1-20.5). A total of 80% of patients initially received the full regorafenib dose of 160 mg once daily for the first 3 weeks of a 4-week cycle. Half of patients required a dose reduction or interruption. The median time to the first treatment modification was 0.7 months (range, 0.03-6.01). Among patients starting cycles 3 and 4, the full regorafenib dose was administered to 50% and 39%, respectively.

After a median follow-up of 16.5 months (range, 1 day to 21.9 months), the median overall survival was 5.6 months (IQR, 2.4-11.4), and 22% of patients were alive at 12 months. Several factors were associated with reduced survival, including low body mass index, an ECOG performance status higher than 0, management in university/comprehensive cancer centers or general hospitals, a short time since the diagnosis of metastases, the presence of synchronous or liver metastases, a high number of metastatic sites, a low initial dose of regorafenib, a short time since receiving prior bevacizumab, and the presence of KRAS mutations. Of these factors, a multivariate analysis showed an independent association with reduced overall survival for higher ECOG performance status, shorter time since initial diagnosis, low initial daily dose, number of metastatic sites, presence of liver metastases, and the presence of KRAS mutations.

As mentioned, the median overall survival for regorafenib in the CORRECT trial was 6.4 months. The authors suggested that the lower duration seen in the REBECCA study might be attributable to the less stringent enrollment criteria that reflected a real-world population. For example, the REBECCA trial permitted enrollment of patients with any ECOG performance status (whereas the CORRECT trial limited ECOG performance status to 0 or 1). An exploratory post hoc analysis from the REBECCA trial identified a subset of patients with similar characteristics to those enrolled in the CORRECT study population. These patients had a median overall survival of 6.3 months, which was similar to the median overall survival of 6.4 months seen in the CORRECT trial.

In the REBECCA study, the median PFS was 2.7 months, which is longer than the 1.9 months seen in the CORRECT trial.14 The study authors noted that this finding should be cautiously interpreted owing to the longer median time to first tumor assessment reported in the real-world study population.

Overall, 80% of patients developed at least 1 adverse event that was related to regorafenib. The most common regorafenib-related adverse events of any grade were fatigue (41.4%), hand-foot skin reaction (28.9%), diarrhea (18.8%), and anorexia (14.7%). The most frequent grade 3/4 regorafenib-related adverse events were fatigue (14.5%) and hand-foot skin reaction (9%). Interestingly, the median overall survival was 7.7 months in patients who developed hand-foot skin reaction vs 4.1 months in those who did not.

The Japanese Postmarketing Surveillance Study

Yamaguchi and colleagues reported on the findings from a large, prospective, multicenter, observational postmarketing surveillance study that evaluated the safety and efficacy of regorafenib for the treatment of mCRC in real-world conditions in a Japanese population. A total of 1227 patients were evaluated between March 2013 and May...
2015. Criteria that were strongly considered for excluding patients from treatment included evidence of severe liver injury (AST or ALT >5 times the upper limit of normal [ULN], bilirubin >2.0 times the ULN), uncontrolled hypertension, or an ECOG performance status of 2 or higher. At baseline, the patients’ median age was 65 years, and 59% were male. The ECOG performance status was 0 in 43.6%, 1 in 48.0%, and 2 or higher in 8.3%. A total of 51.2% had wild-type KRAS status. Prior systemic therapies numbered 4 in 25.4%, 3 in 36.8%, and 1 or 2 in 37.8%. Bevacizumab was a prior therapy for 91.0%. Patients had also received anti-EGFR therapy, including 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. Dose modifications were made according to the recommendations from the regorafenib label. Approximately two-thirds of patients initiated regorafenib at the standard dose of 160 mg once daily (65.4%). The remaining patients initiated treatment at a daily dose of 120 mg (21.6%) or lower (13.0%).

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. In 33% of patients, treatment was discontinued owing to an adverse event for which a causal relationship with regorafenib could not be excluded (abbreviated as ADR). Grade 3 or higher ADRs were reported in 51.8% of patients. The most frequent of these events were hand-foot skin reaction in 19.2%, hypertension in 15.6%, liver injury in 11.5%, thrombocytopenia in 4.7%, and decreased appetite in 2.7%. The most common ADR of any grade was hand-foot skin reaction, reported in 58.2% of patients, followed by liver injury in 31.4% and hypertension in 28.8%.

A landmark analysis identified several factors with a significant effect on overall survival. Factors associated with an overall survival benefit 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 m² as estimated by the Du Bois formula.

The authors of this postmarketing surveillance study concluded that the efficacy observed in this real-world cohort was consistent with experience in the phase 3 clinical trials.

The IMblaze370 Study

The phase 3 IMblaze370 study (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma) evaluated the immune checkpoint inhibitor atezolizumab, administered either alone or with the addition of the targeted agent cobimetinib, in comparison to regorafenib as the standard of care. Although the goal of this study was to determine the efficacy and safety of a novel immunotherapy combination in mCRC, it provided important data regarding regorafenib. The rationale for the study design was based on preclinical and early clinical data, which suggested that while microsatellite instability–high (MSI-H) mCRC is sensitive to inhibition of the PD-1/PD-L1 immune checkpoint, microsatellite-stable disease is largely unresponsive to this class of immunotherapy. However, microsatellite-stable disease accounts for most cases of mCRC; therefore, efforts have focused on how to make microsatellite-stable disease more sensitive to immune checkpoint inhibition.

The IMblaze370 study was a multicenter, open-label, randomized, controlled phase 3 trial that enrolled patients across 11 countries. All patients had unresectable, locally advanced CRC or mCRC. They had developed disease progression after treatment with at least 2 prior systemic chemotherapy regimens (containing fluorouracil, oxaliplatin, and irinotecan), or they were intolerant to these treatments. Enrollment of patients with MSI-H tumors was limited to approximately 5%, reflecting the real-world patient population. At baseline, patients had an ECOG performance status of 0 or 1, a life expectancy of at least 3 months, and adequate organ function.

Patients were randomly assigned in a 2:1:1 fashion to treatment with atezolizumab (840 mg every 2 weeks) plus cobimetinib (60 mg once daily on days 1-21 of a 28-day cycle), atezolizumab monotherapy (1200 mg every 3 weeks), or regorafenib (160 mg once daily on days 1-21 of a 28-day cycle). Treatment was continued until unacceptable toxicity or loss of clinical benefit as assessed by the investigator. Treatment could continue beyond radiographic progression, as these heavily pretreated patients had limited alternative therapeutic options.

A total of 363 patients were randomly assigned to treatment between July 2016 and January 2017. Baseline characteristics were well balanced across the 3 treatment arms. The median patient age ranged from 56 to 59 years,
and 60% were male. The ECOG performance status was 0 in 48% and 1 in 52%. A total of 1.6% of the population had MSI-H disease (with no cases in the regorafenib arm). Notably, 74% of the study population had received 3 or fewer lines of treatment, and 26% had received more than 3 lines of prior therapy. Most patients (87%) had received prior treatment with an anti-VEGF and/or an anti-EGFR targeted therapy.

After a median follow-up of 7.3 months, the IMblaze370 study did not meet its primary endpoint of an improvement in overall survival. The median overall survival did not differ significantly between any of the treatment arms. The median overall survival was 8.87 months with atezolizumab plus cobimetinib, 7.10 months with atezolizumab monotherapy, and 8.51 months with regorafenib. The HR for survival was 1.00 (95% CI, 0.73-1.38; \( P = .99 \)) for the combination vs regorafenib, and 1.19 (95% CI, 0.83-1.71; \( P = .34 \)) for atezolizumab monotherapy vs regorafenib.

The results of IMblaze370 showed that regorafenib offered a similar survival benefit as compared with a novel immunotherapy combination. Additionally, the study authors noted that the median overall survival of 8.51 months seen with regorafenib exceeded the projected duration of 6.4 months made during the study design (based on the CORRECT study). Although cross-trial comparisons cannot be made, it is notable that 74% of patients in the IMblaze370 trial had received 3 or fewer lines of treatment, making them a relatively less heavily pretreated population than those in the CORRECT study. Among patients in the CORRECT study, 52% had received 3 or fewer lines of treatment, and the remaining 48% had received 4 or more lines of therapy. These data therefore provide evidence suggesting that earlier incorporation of regorafenib may improve survival.

The REVERCE Study

The randomized phase 2 REVERCE trial (A Randomized Phase II Study of Regorafenib Followed by Cetuximab Versus the Reverse Sequence for Wild-Type KRAS Metastatic Colorectal Cancer Previously Treated With Fluoropyrimidine, Oxaliplatin, and Irinotecan. Adapted from Shitara K et al. ASCO abstract 3510. Ann Oncol. 2019;30(2):259-265.) compared regorafenib followed by cetuximab (R-C) vs cetuximab followed by regorafenib (C-R) among patients with metastatic colorectal cancer. Median overall survival is shown. 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. ASCO abstract 3510. Ann Oncol. 2019;30(2):259-265.)
2 wild-type disease. Patients were randomly assigned to treatment with regorafenib followed by cetuximab (administered with or without irinotecan), or the reverse sequence (cetuximab with or without irinotecan first, followed by regorafenib).

The primary endpoint was overall survival. Key secondary endpoints included PFS with initial treatment, PFS with second treatment, safety, and quality of life. The median overall survival was 17.4 months for regorafenib followed by cetuximab, and 11.6 months for cetuximab followed by regorafenib (HR, 0.61; 95% CI, 0.39-0.96; \( P = .0293 \); Figure 4). The HR for PFS was 0.97 (95% CI, 0.61-1.54) with the initial treatment and 0.29 (95% CI, 0.17-0.50) with the second treatment.

No unexpected toxicities occurred. There were no significant differences apparent in quality-of-life scores during the entire treatment period between the 2 arms. Circulating biomarker analyses (an exploratory endpoint) showed more frequent detection of potentially emerging oncogenic alterations (eg, in \( RAS \), \( BRAF \), \( EGFR \), \( HER2 \), and \( MET \)) following cetuximab treatment (compared with regorafenib treatment).

The study authors observed that the median overall survival reported with regorafenib sequenced with cetuximab was greater than that reported in the pivotal phase 3 trials. However, it should be noted that in the REVERCE study, exposure to regorafenib occurred far earlier in the course of treatment.
The ReDOS Trial

The standard dosing regimen of regorafenib, 160 mg once daily, can be associated with toxicities, such as fatigue and hand-foot skin reaction (Figure 5). The randomized phase 2 ReDOS trial (Regorafenib Dose Optimization Study) evaluated whether toxicities could be minimized with a regimen that began with a lower dose and then gradually escalated to the standard dose.8,9 The trial randomly assigned 123 patients to a dose-escalation arm or a standard-dose arm, and 116 patients were evaluable for treatment. In the dose-escalation arm, treatment began with 80 mg once daily on days 1 to 7. The dose of regorafenib was escalated to 120 mg once daily on days 8 to 14, then to 160 mg once daily on days 15 to 21, and then continued at 160 mg once daily every 3 weeks out of each subsequent 4-week treatment cycle. Patients in the standard-dose arm received the approved dose of 160 mg once daily.

The primary endpoint was the proportion of evaluable patients (defined as those who were eligible, consented, and received any protocol treatment) initiating cycle 3. At baseline, the patients’ median age was 61.5 years. More than half of patients (61.5%) were male. The ECOG performance status was 1 in 63%. Three or more metastatic sites were reported in 67.5% of patients, and 47% had KRAS-mutated disease.

The study met its primary endpoint. The percentage of patients initiating treatment cycle 3 was 43% in the dose-escalation arm vs 26% in the standard-dose arm (1-sided \(P=0.043\)).9

The median overall survival was 9.8 months in the dose-escalation arm vs 6.0 months in the standard-dose arm, a difference that did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank \(P=0.12\); Figure 6). The median PFS was 2.8 months in the dose-escalation arm vs 2.0 months in the standard-dose arm, a difference that was not significant (HR, 0.84; 95% CI, 0.57-1.24; log-rank \(P=0.38\)).

The most common grade 3 to 4 adverse events were fatigue (seen in 13% of the dose-escalation group vs 18% in the standard-dose group), abdominal pain (17% vs 6%), hand-foot skin reaction (15% vs 16%), and hypertension (7% vs 15%). At least 1 drug-related serious adverse event occurred in 6 patients in the dose-escalation group and 8 patients in the standard-dose group.

Disclosure

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

References

Current and Future Research Into the Mechanism of Action of Regorafenib

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There are 2 exciting areas of investigation into the use of regorafenib for the treatment of mCRC. One area is patients with MSI-H disease, who have a reduced response to chemotherapy and therefore a particularly poor prognosis. Researchers are attempting to determine the role of regorafenib in these patients. A second major line of investigation is how to exploit the immunomodulatory mechanism of regorafenib and determine its efficacy and safety in combination with immune checkpoint inhibitor therapy.

New Research Into MSI-H mCRC: Exploratory Analysis of the CORRECT Study

MSI-H status has been associated with a good prognosis in early-stage CRC. However, mCRC does not seem to show the same association, as emerging evidence suggests that MSI-H status is associated with a worse response to chemotherapy in this setting. This observation prompted investigators to conduct an exploratory analysis of the CORRECT study to evaluate overall survival outcomes.

Figure 7. Best tumor response among patients with colorectal cancer treated in the phase 1b REGONIVO trial of regorafenib plus nivolumab. a New lesion. b MSI-H (all other patients were MSS). MSI-H, microsatellite instability–high; MSS, microsatellite stable; ORR, overall response rate; PD, progressive disease; PR, partial response; REGONIVO, Regorafenib and Nivolumab Simultaneous Combination Therapy; SD, stable disease. Adapted from Fukuoka S et al. ASCO abstract 2522. J Clin Oncol. 2019;37(suppl 15).2
by baseline MSI status in patients with mCRC. This analysis was performed using archival tissue specimens. MSI status was determined by next-generation sequencing of archival tumor, using the FoundationONE gene panel (Foundation Medicine).

Archived tumor tissue was available for 229 patients. Among this subgroup, 62% were male. The ECOG performance status was 0 in 57% and 1 in 43% A KRAS mutation was identified in 58%, and 3% had a BRAF mutation. The analysis defined 42 patients (18%) as MSI-H and 187 (82%) as non–MSI-H (referred to as MSI-stable). Overall, clinical benefit was lower among patients who were MSI-H vs MSI-stable. A multivariate analysis, however, showed no significant association between MSI status and overall survival or PFS (P=.15). The HR for overall survival was 0.97 (95% CI, 0.45-2.07) in the MSI-H group and 0.78 (95% CI, 0.53-1.15) in the MSI-stable group. The HR for disease progression or death was 0.78 (95% CI, 0.39-1.56) in the MSI-H group and 0.48 (95% CI, 0.35-0.67) in the MSI-stable group.

The authors of this exploratory analysis concluded that there was no significant interaction between MSI status and benefit with regorafenib. They also noted, however, that the small number of patients in the subgroups limited the conclusions, suggesting that further studies are necessary to assess the correlation between MSI status and regorafenib clinical benefit.

**Combination of Regorafenib With Immune Checkpoint Therapy: The REGONIVO Study**

The REGONIVO study was an open-label, dose-finding, dose-expansion phase 1b trial that evaluated the combination of regorafenib with the anti–PD-1 immunotherapy nivolumab for the treatment of mCRC or advanced gastric cancer. Regorafenib plus nivolumab was administered in a 3+3 design. The daily dose of regorafenib ranged from 80 mg to 160 mg (administered for 3 weeks out of a 4-week cycle). Nivolumab was administered at a constant dose of 3 mg/kg every 2 weeks. The dose-expansion cohort consisted of 36 patients.

The study enrolled patients who had histologically or cytologically confirmed advanced or metastatic CRC or gastric cancer, with evaluable or measurable lesions. Patients were refractory to or intolerant of standard chemotherapy. An ECOG performance status of 0 or 1 was required.

The REGONIVO study enrolled 50 patients across both the dose-escalation and dose-expansion portions. The patients’ median age was 60.5 years, and 80% were...
male. Half of patients had CRC, and the other half had gastric cancer. The ECOG performance status was 0 in 98% of patients. Prior to study enrollment, patients had received a median of 3 prior regimens (range, 2 to 8), including an angiogenesis inhibitor in 96% and an anti–PD-1/PD-L1 agent in 14%.

During the dose-escalation phase, the highest dose of regorafenib was associated with dose-limiting toxicities, including grade 3 rash (n=1), grade 3 proteinuria (n=1), and grade 3 colonic perforation (n=1). The maximum tolerated dose of regorafenib was identified as 120 mg once daily when combined with nivolumab. In the dose-expansion cohort, however, the dose of regorafenib was reduced from 120 mg to 80 mg. Therefore, 80 mg once daily was considered the optimal dose for future studies of regorafenib in combination with nivolumab.

The median duration of treatment was 6.1 months (range, 0.7-14.9). Among the 50 patients enrolled in the REGONIVO study, the most frequent treatment-related adverse events of any grade were hand-foot skin reaction (70%), hypertension (48%), fatigue (46%), rash (42%), and fever (40%). The most frequent grade 3 or higher treatment-related adverse events were rash (12%), proteinuria (12%), and hand-foot skin reaction (10%).

Across all 50 patients, the objective response rate was 40% (95% CI, 26%-55%), and the disease control rate was 88% (95% CI, 76%-96%). The objective response rate was 45% with the 80-mg once daily dose, 36% with the 120-mg once daily dose, and 33% with the 160-mg once daily dose. Specifically among patients with CRC, the objective response rate was 36% (Figure 7), and the median PFS was 6.3 months (Figure 8).

Interestingly, flow cytometry analysis of tumor-infiltrating lymphocytes showed a marked decrease in Treg cells following treatment with the combination of regorafenib plus nivolumab, in contrast to when nivolumab was used alone. This finding is notable, as Treg cells can dampen the antitumor immune response and limit the effectiveness of PD-1/PD-L1 checkpoint inhibition. Thus, these data suggest that the addition of regorafenib may help to overcome this mechanism of tumor evasion of the immune response.

The REGONIVO investigators concluded that the combination of regorafenib and nivolumab was associated with a manageable safety profile and promising anti-tumor activity. The authors stated that these results supported the further development of this combination in a larger cohort of patients. The REGONIVO study had some important limitations. Most notably, it was a small study, and it enrolled only Japanese patients. Global confirmation is therefore needed, and results from an ongoing US trial are expected soon.

Disclosure
Dr Yoshino has received research funding from Novartis Pharma KK, MSD KK, Sumitomo Dainippon Pharma, Chugai Pharmaceutical, Sanofi KK, Daiichi Sankyo, Parexel International, and Ono Pharmaceutical.

References
1. Köchert K, Beckmann G, Teufel M. Exploratory analysis of baseline microsatellite instability (MSI) status in patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) or placebo in the phase 3 CORRECT trial. Ann Oncol. 2017;28(suppl 5):534P.

The Mechanism of Action of Regorafenib in Colorectal Cancer: Q&A

Axel Grothey, MD, Gerald Prager, MD, and Takayuki Yoshino, MD

Dr Grothey The data for regorafenib are intriguing, particularly regarding its interaction with the anticancer immune response and use in earlier lines of therapy. Of course, an issue that we face when using this agent is the perceived toxicity profile. Dr Prager, I would like to have your input about the emerging dosing strategies (Figure 9). Have these data impacted your clinical practice? Do you believe that a modified dosing schedule could enhance the use of regorafenib either alone or in combination with other agents?

Dr Prager The ReDOS study clearly demonstrated that when initiating treatment with 80 mg once daily, it is possible to find a patient’s individual tolerance by rapidly accelerating the dose in the second week to 120 mg and then in the third week to 160 mg in the absence of severe toxicity. The ReDOS study showed that the proportion of patients who completed 2 cycles of therapy and initiated cycle 3 was significantly higher in the dose-escalation group than in the standard-dose group. This finding may be explained not only by a better toxicity profile, but also...
by the possibility that starting at the lower dose may allow for immune system modulation without provoking high-grade toxicity.

**Dr Grothey** Dr Yoshino, how does the mechanism of action of regorafenib impact the sequencing of this agent, particularly when the goal is to expose the patient to as many active agents as possible?

**Dr Yoshino** As has been discussed, regorafenib has multiple mechanisms of action, and it can exert a 4-pronged strategy against tumors consisting of anti-angiogenesis, anti-oncogenesis, anti-metastasis, and anti-immunosuppression. One potential option to consider, particularly with the increasing understanding of regorafenib as an immunomodulatory agent, is to use regorafenib as a maintenance treatment in the first-line setting. The REGONIVO trial and similar studies are evaluating regorafenib in combination with nivolumab in patients with mCRC and disease progression.3

**Dr Grothey** Dr Prager, we talked about the interaction of regorafenib and the immune system. The Japanese REGONIVO trial combined regorafenib with nivolumab,1 and this combination will now be explored in a broader population. What are some other exciting areas of research?

**Dr Prager** The REVERCE data demonstrated that regorafenib followed by cetuximab led to greater clinical activity than the other way around.4 Cetuximab is acting via antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Thus, regorafenib may potentially convert an immune “cold” tumor to an immune “hot” tumor. It would be interesting to see more preclinical as well as clinical data on this subject.

**Dr Grothey** This research also provides a glimpse into the evolution of immuno-oncology. Currently, most discussion in immuno-oncology is focused on the use of antibodies directed against the PD-1/PD-L1 and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) checkpoints. However, the anticancer immune response involves far more complicated mechanisms. I hope that over time, more preclinical and clinical data will emerge that provide access to new immuno-oncology combinations and options beyond these checkpoint inhibitors. Regorafenib could emerge as an interesting combination partner.

**Dr Yoshino** Additionally, early data from REGONIVO showed that even patients with previous exposure to anti-PD-1/PD-L1 treatment have a similar benefit with regorafenib plus nivolumab.3 This offers further support to the concept that regorafenib converts a tumor from immune-cold to immune-hot, as Dr Prager mentioned.

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**Figure 9.** An incremental dose-escalation protocol for regorafenib has been shown to decrease toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. Clin Adv Hematol Oncol. 2015;13(8):514-517.1
Dr Grothey Dr Yoshino, for the community physician, how would you explain the role for regorafenib in the management of patients in the third-line setting in mCRC?

Dr Yoshino In my opinion, regorafenib at the standard dose of 160 mg once daily for 3 weeks of a 4-week cycle is simply too toxic for patients. In our experience, more than 90% of Japanese patients reduce their dose to 120 mg or 80 mg. Currently, based on the ReDOS data, an initial dose of 80 mg to 120 mg is optimal for later-line single-agent regorafenib.

REARRANGE (Study Comparing Different Dose Approaches of Induction Treatment of Regorafenib in MCRC) is a European study that compared the standard dose of regorafenib vs 2 dosing strategies: either escalation from a low dose to an elevated dose or an intermittent dosing schedule. The results were recently reported. In this trial, both experimental arms showed a numeric improvement in relevant adverse events, such as fatigue and hypertension, without jeopardizing efficacy (Table 2). The study did not show a statistically significant improvement in tolerability for the reduced or intermittent dosing arms vs the standard arm. However, these data support the use of an initial reduced dosing schedule of regorafenib during the first cycle.

There is also the possibility that regorafenib can be used after anti–PD-1 monotherapy in MSI-high patients who are refractory after progression. In the near future, it may be that these patients would simply continue their anti–PD-1 therapy even after progression, adding on low-dose regorafenib in order to change their immunosuppressive condition.

Dr Prager I would like to see combinations of regorafenib plus immunotherapy used in other settings in addition to mCRC and gastric cancer. The next candidate, in my opinion, would be hepatocellular carcinoma. In hepatocellular carcinoma, I would like to see an active agent such as regorafenib combined with an active immunotherapy, such as nivolumab. We can also think beyond gastrointestinal cancer indications. It would be interesting to see the potential benefit in other solid tumor types that are classically considered immune-cold. It will be important to see if regorafenib could modulate the immune system as an immune sensitizer in these different indications, converting the immune-cold tumors to immune-hot. This is indeed a very exciting time for regorafenib and for immunotherapy, with many different approaches ready to be tested in clinical trials.

Disclosures
Dr Grothey’s institution has received honoraria for consulting activities from Bayer, Roche/Genentech, Array, Boston Biomedical, and Caris. He has received travel support from Bayer, Roche/Genentech, and Array. Dr Prager has attended advisory board meetings/symposiums for Merck Serono, Roche, Amgen, Sanofi, Lilly, Servier, Taiho, Bayer, Halozyme, BMS, Celgene, and Shire. Dr Prager’s institution has received funding for clinical trials from Celgene, Array, Servier, Bayer, Boston Biomedical, Merck, and BMS. Dr Yoshino has received research funding from Novartis Pharma KK, MSD KK, Sumitomo Dainippon Pharma, Chugai Pharmaceutical, Sanofi KK, Datichi Sankyo, Parexel International, and Ono Pharmaceutical.

References

Table 2. The Most Common Grade 3/4 Adverse Events in the REARRANGE Trial of Regorafenib

<table>
<thead>
<tr>
<th>Event</th>
<th>Standard Dose (%)</th>
<th>Reduced Dose (%)</th>
<th>Intermittent Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3, 4, and 5 adverse events</td>
<td>61</td>
<td>57</td>
<td>55</td>
</tr>
<tr>
<td>Asthenia and fatigue</td>
<td>20</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>8</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>2</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

‘Occurring in >4% of patients. REARRANGE, Study Comparing Different Dose Approaches of Induction Treatment of Regorafenib in MCRC. Adapted from Argilés G et al. ESMO-GI abstract O-026. Ann Oncol. 2019;30(suppl 4).’
Regorafenib: Mechanisms of Action

- Regorafenib is not a traditional cytotoxic chemotherapy
- Regorafenib is a multi-targeted therapy, with a mechanism of action that inhibits various aspects of tumor biology and tumor-host interaction
- Regorafenib is a small molecule that inhibits multiple membrane-bound and intracellular kinases involved in normal cellular functions and pathologic processes, such as tumor angiogenesis, metastasis, oncogenesis, and tumor immunity

Regorafenib: Angiogenesis

- Regorafenib inhibits VEGFRs 1, 2, and 3
- Regorafenib also inhibits FGFRs 1 and 2, the angiopoietin-1 receptor TIE2, and PDGFR α and β
- Both FGFR and PDGFR have emerged as potential mechanisms of resistance in tumors that begin to show proliferation despite anti-VEGF pathway inhibition

FGFRs, fibroblast growth factor receptors; PDGFR, platelet-derived growth factor receptor; VEGFRs, vascular endothelial growth factor receptors.

Regorafenib: Metastasis

- Inhibition of tumor metastasis is thought to occur through both antiangiogenic and antiproliferative mechanisms
- Inhibition of VEGFR2-mediated signaling by regorafenib induces a reduction of microvessels and increases apoptosis
- Inhibition of VEGFR3 may help reduce metastatic spread by blocking tumor lymphangiogenesis and preventing endothelial sprouting and vascular network formation

Regorafenib: Oncogenesis

- Regorafenib blocks multiple oncogenic pathways, including RAF-1, RET, and KIT
- Inhibition of these signal transaction pathways in cancer cells can inhibit cell proliferation and survival signaling, and increase pro-apoptotic signaling pathways

Regorafenib: Tumor Immunity

- Regorafenib appears to show immunomodulatory properties
- Regorafenib inhibits CSF1R, a tyrosine kinase receptor that is involved in macrophage proliferation. Macrophages are generally thought to be part of the immunostimulatory response, but macrophages can in fact both stimulate and inhibit the immune response
- It is hypothesized that regorafenib may work in concert with anti-PD-1/PD-L1 antibodies to augment the anticancer immune response

PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

The REGONIVO Study

- The REGONIVO study was an open-label, dose-finding, dose-expansion phase 1b trial that evaluated the combination of regorafenib with the anti-PD-1 immunotherapy nivolumab for the treatment of mCRC.
- Patients with advanced gastric cancer were also enrolled
- Among patients with mCRC, the objective response rate was 36%, and the median progression-free survival was 6.3 months
- The investigators concluded that the combination of regorafenib and nivolumab was associated with a manageable safety profile and promising anti-tumor activity

mCRC, metastatic colorectal cancer.

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