Optimized Dosing of Regorafenib in Patients With Metastatic Colorectal Cancer: A Practical Guide for Oncologists, Advanced Practice Providers, and Pharmacists

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Abstract

The multikinase inhibitor regorafenib has improved outcomes for patients with metastatic colorectal cancer (mCRC) following failure of standard therapies. However, regorafenib may be associated with treatment-emergent adverse events (TEAEs) requiring dose modifications. The regorafenib dose-optimization study (ReDOS) investigated a systematic method for titrating regorafenib up to the highest tolerable dose through a prospective evaluation of a first-cycle dose-escalation strategy, compared with standard dosing in patients with refractory mCRC. ReDOS met its primary endpoint, with more patients starting cycle 3 in the dose-escalation group (43%) vs. the standard-dose group (26%; $p = .043$). The safety profile was consistent with previous reports, and the incidence of regorafenib-related grade 3 TEAEs was generally lower in the dose-escalation group vs. the standard-dose group in cycles 1 and 2. Secondary endpoints showed that dose escalation did not negatively impact efficacy. Initiating regorafenib below the approved standard dose (160 mg/day) improves tolerability and allows health-care professionals to individualize the dose during cycles 1 and 2 without reducing overall drug exposure. This strategy provides an evidence-based guide to optimize regorafenib dosing and improve tolerability without compromising efficacy, allowing patients to remain on regorafenib for longer and potentially improve outcomes. This review provides a clinically relevant appraisal of ReDOS and the implications for patient management from the perspective of oncologists, advanced practice providers, and pharmacists.

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Outcomes for patients with refractory metastatic colorectal cancer (mCRC) have improved markedly, partly due to new treatment options and better patient management (Bekaii-Saab et al., 2019a; Cervantes et al., 2023). First-line treatment usually consists of oxaliplatin- or irinotecan-based chemotherapy and targeted treatments, including angiogenesis inhibitors or anti-epidermal growth factor receptor monoclonal antibodies in patients with *RAS* wild-type tumors (Cervantes et al., 2023). Recently, immune checkpoint inhibitors (for patients with high microsatellite instability and high tumor mutational burden), kinase inhibitors targeting the BRAF protein (in patients with *BRAF* V600E mutations), and anti-human epidermal growth factor receptor-2 (HER2) antibodies (for patients with HER2 overexpression) have been introduced (Cervantes et al., 2023; Schrock et al., 2019). In addition to new therapies, management by a multidisciplinary team (MDT) may contribute to improved outcomes. The MDT includes advanced practice providers (APPs) and pharmacists, facilitating the implementation of "continuum of care" management strategies, along with the early integration of optimal supportive care measures, which is important in mCRC, as patients often receive three or more lines of therapy and continue to benefit from later treatment lines (Bekaii-Saab et al., 2019a; Cervantes et al., 2023). To increase overall survival (OS), patients should be given an opportunity to receive all available treatment options as part of the continuum of care (Cervantes et al., 2023).

For patients who have progressed after standard fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy, regorafenib (Stivarga) provides an option for continued therapy (Bayer AG, 2023; Bayer HealthCare Pharmaceuticals, 2020; Bekaii-Saab et al., 2019a). Regorafenib targets kinases involved in tumor angiogenesis and has immunomodulatory activity (Abou-Elkacem et al., 2013; Schmieder et al., 2014; Wilhelm et al., 2011; Zopf et al., 2016). Optimal dosing and the management of adverse events (AEs) are critical to allow patients to remain on treatment and derive maximum clinical benefit (Grothey, 2015; Van Cutsem et al., 2019).

The efficacy of regorafenib in mCRC has been established from clinical trials and real-world studies. Two randomized, controlled, phase III clinical trials (CORRECT and CONCUR) showed that regorafenib improved OS, progression-free survival (PFS), and disease control vs. placebo in patients with treatment-refractory mCRC (Grothey et al., 2013a; Li et al., 2015). In CORRECT, median OS was 6.4 vs. 5.0 months (hazard ratio [HR], 0.77; $p = .0052$; Grothey et al., 2013b). The CONCUR trial confirmed the OS benefit of regorafenib in Asian patients, with a median OS of 8.8 vs. 6.3 months (HR, 0.55; $p = .00016$; Li et al., 2015). Subsequently, the large ($N = 2,872$), prospective, international, single-arm, phase IIIb CONSIGN study found that the median PFS in patients receiving regorafenib (2.7 months) was consistent with that reported in phase III trials (Van Cutsem et al., 2019). Overall survival and PFS values in the range of those obtained in interventional trials have also been obtained with regorafenib in prospective observational studies (Ducreux et al., 2019; Eng et al., 2019; Kopeckova et al., 2017; Lai et al., 2021; Nannini et al., 2021; Novakova-Jiresova et al., 2020; Yamaguchi et al., 2019).

Although regorafenib confers survival benefit, it is associated with treatment-emergent adverse events (TEAEs), frequently requiring dose reductions or interruptions and, occasionally, permanent treatment discontinuation (Ducreux et al., 2019; Grothey et al., 2013a; Grothey et al., 2013b; Li et al., 2015; Van Cutsem et al., 2019). The most common regorafenib-related TEAEs in CORRECT and CONCUR included hand–foot skin reaction (HFSR), fatigue, hypertension, and diarrhea (Grothey et al., 2013b; Li et al., 2015). A similar TEAE profile was observed in CONSIGN and the real-world CORRELATE study (Ducreux et al., 2019; Van Cutsem et al., 2019); however, the incidence of individual TEAEs was lower in CORRELATE partly due to potential underreporting given the observational nature of the study, more effective AE management, and because approximately half of the patients initiated regorafenib at < 160 mg/day (Ducreux et al., 2019). Notably, regorafenib-related AEs, such as HFSR and fatigue, occur early following treatment initiation (usually within the first cycle), and their severity decreases over time (Grothey et al., 2013a).

The approved dose of regorafenib for treatment-refractory mCRC is 160 mg/day orally for the first 3 weeks of each 4-week cycle (Bayer AG, 2023; Bayer HealthCare Pharmaceuticals, 2020). In clinical practice, different dose-reduction strategies have been used to increase tolerability and allow patients to remain on treatment, which appears to be critical to maximize the therapeutic potential of a cytostatic agent like regorafenib (Bruix et al., 2017; Demetri et al., 2013; Ducreux et al., 2019; Grothey et al., 2013b). Until recently, these approaches had not been assessed in randomized trials. The regorafenib dose-optimization study (ReDOS) aimed to establish a systematic approach to titrating regorafenib up to the highest tolerable dose (Bekaii-Saab et al., 2019b). The study prospectively evaluated in treatment-refractory mCRC a structured strategy of dose escalation over the first cycle compared with initiation at the standard dose (Bekaii-Saab et al., 2019b).

As integral members of the MDT, APPs and pharmacists play a fundamental role, not only in managing AEs, but also in ensuring patient adherence to treatment with oral oncology drugs and in overcoming ongoing drug supply or reimbursement challenges that present a barrier to patients' access to medicines. Continued patient education and support are vital to ensure that patients achieve the best possible outcomes from treatment.

This review aims to provide a clinically relevant appraisal of the outcome of ReDOS and the implications for patient treatment and support from the perspective of oncologists, APPs, and pharmacists.

REGORAFENIB DOSING AND THE RATIONALE FOR ReDOS

In CORRECT, CONCUR, and CONSIGN, the regorafenib starting dose was 160 mg/day for the first 3 weeks of each 4-week cycle (Grothey et al., 2013b; Li et al., 2015; Van Cutsem et al., 2019). The dose could be reduced (to 80 mg), interrupted, or permanently discontinued to manage treatment-related toxicities, with reescalation up to 160 mg after TEAEs resolved. Treatment was discontinued permanently if TEAEs did not resolve following treatment delay or dose reductions. Across the three trials, TEAEs led to regorafenib treatment modifications in > 60% of patients, including 38% to 46% of patients who had a TEAE leading to a dose reduction (Grothey et al., 2013b; Li et al., 2015; Van Cutsem et al., 2019). In CONCUR and CONSIGN, fewer patients (14% to 25%) discontinued treatment due to TEAEs, suggesting that dose modifications allowed some patients to remain on therapy (Li et al., 2015; Van Cutsem et al., 2019). Similarly, clinical studies of regorafenib in gastrointestinal stromal tumors or hepatocellular carcinoma (HCC) show that regorafenib-associated TEAEs were largely managed with dose modifications or interruptions (Bruix et al., 2017; Demetri et al., 2013).

In real-world practice, the dose of regorafenib is often modified or interrupted in response to TEAEs, consistent with clinical trial protocols and current prescribing information (Bayer AG, 2023; Bayer HealthCare Pharmaceuticals, 2020; Grothey et al., 2013b). However, different dosing strategies are being used without the support of prospective clinical trial evidence. Many physicians reported starting regorafenib below the approved dose (i.e., 80 or 120 mg/day) in cycle 1 and then up-titrating to improve tolerability (Grothey, 2015; Tabchi & Ghosn, 2015). Evidence from real-world studies shows that over one-third of patients start regorafenib below the approved dosage (Ducreux et al., 2019; Yamaguchi et al., 2019). The frequent need for dose reductions when starting regorafenib at 160 mg/day, coupled with the use of proactive dose-titration strategies in real-world practice, motivated the design of ReDOS (Bekaii-Saab et al., 2019b). The structured dose-escalation strategy used during cycle 1 was based on exploratory analyses of CORRECT and CONSIGN, showing that the most common regorafenib-related TEAEs, such as fatigue and HFSR, usually occur early and are noncumulative (Grothey et al., 2013a; Van Cutsem et al., 2019). These observations are consistent with the results of a phase III study of regorafenib in HCC (Merle et al., 2017) and with the time course of HFSR related to treatment with other tyrosine kinase inhibitors, including sorafenib (Nexavar) and sunitinib (Sutent), in patients with HCC, renal cell carcinoma, or differentiated thyroid carcinoma (Lacouture et al., 2008; Worden et al., 2015).

Initiating regorafenib below the standard dose would allow the dose to be individualized according

to how well the drug is tolerated during cycle 1. ReDOS included an extensive evaluation of quality of life (QOL). In clinical practice, patients with mCRC often receive regorafenib as a third or fourth line of treatment, at a stage where QOL is paramount.

ReDOS FIRST-CYCLE DOSE-ESCALATION STRATEGY

ReDOS was a randomized phase II study in patients with refractory mCRC and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (Bekaii-Saab et al., 2019b). Patients were randomly assigned to initiate regorafenib at the standard daily dose (n = 62) or at a reduced dose (80 mg), increasing by 40 mg weekly, over 2 weeks, to reach 160 mg/day if tolerated (n = 54; Figure 1).

The primary endpoint was the proportion of patients in each group who completed two cycles of treatment and initiated the third cycle and, therefore, encompassed safety and efficacy parameters. Patients were only allowed to begin cycle 3 if they had tolerated treatment (may have experienced mild-to-moderate, but not significant/debilitating, drug-related toxicities despite dose modification) and had stable disease on the first scan after two treatment cycles (8 weeks). The primary endpoint was achieved, with more patients starting cycle 3 in the dose-escalation group (43%) vs. the standard-dose group (26%; p = .043; Bekaii-Saab et al., 2019b).

Weekly dosing for all patients is summarized in Figure 2. Patients in the dose-escalation group

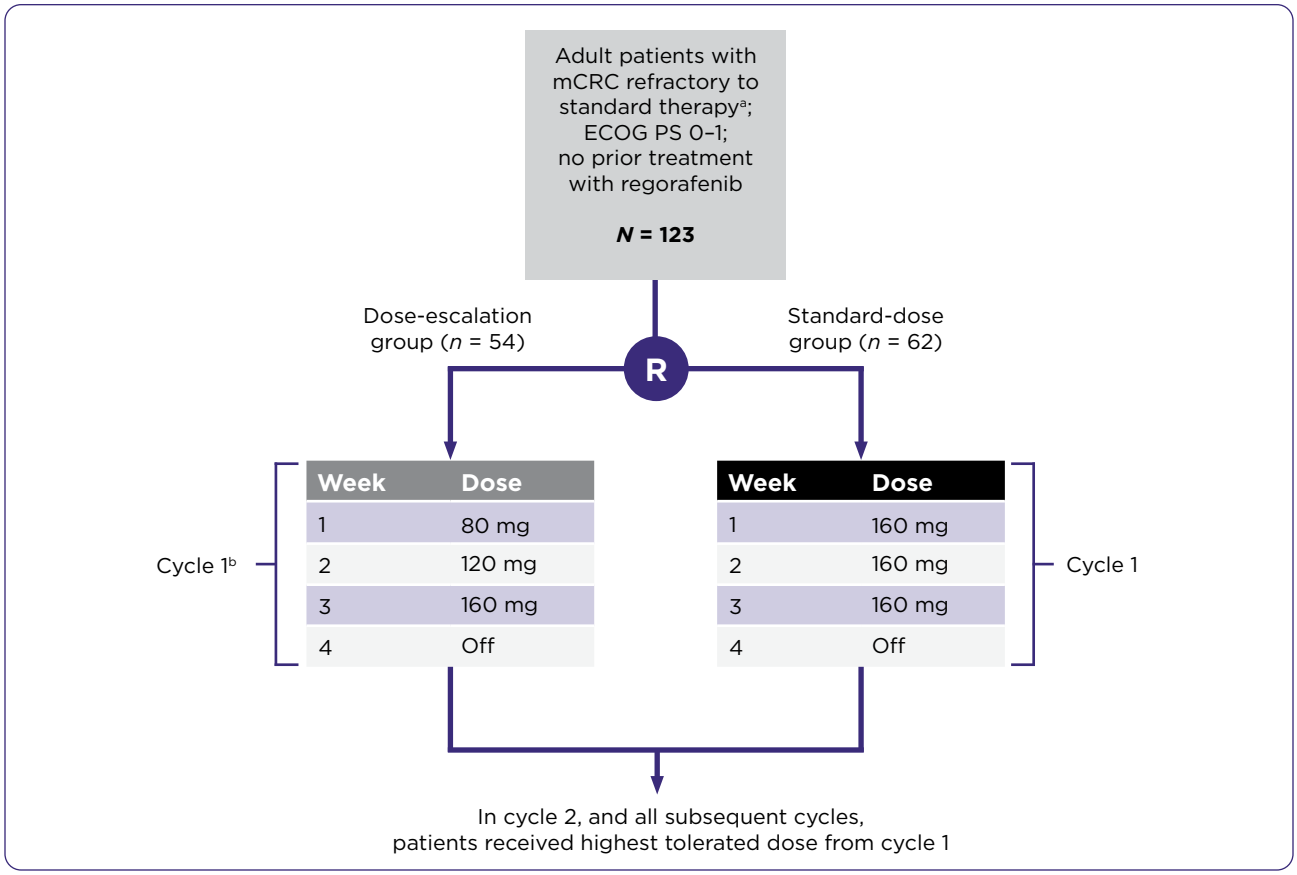

Figure 1. ReDOS dose-escalation strategy. ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; VEGF = vascular endothelial growth factor.
[a]Standard therapy includes fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy and, if *RAS* wild-type, an anti-EGFR therapy.
[b]Weekly incremental dose escalation occurred up to a maximum of 160 mg/day in the absence of significant drug-related toxicity.

Figure 2. Dosing history of individual patients (A: dose-escalation group [*n* = 54]; B: standard-dose group [*n* = 62]) in the ReDOS trial through week 1 of cycle 3. Reprinted from *Lancet Oncology* Volume 20, p. 1070-1082, 2019. Bekaii-Saab TS, et al. Regorafenib dose-optimization in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study, with permission from Elsevier.

received a lower percentage of the planned dose in cycle 1 vs. the standard-dose group (77% vs. 83%, respectively) and a higher percentage in cycle 2 (93% vs. 73%, respectively). Dose modifications in the dose-escalation group and standard-dose group occurred in 24% and 21% of patients in cycle 1, respectively, and in 22% and 32% of patients in cycle 2, respectively. Collectively, the mean dose received was similar in both groups by the end of cycle 2; however, it was individualized in response to tolerability.

The safety profile of regorafenib was consistent with reports from previous clinical trials, and there were no marked differences between the two dosing strategies. However, the incidence of grade 3 TEAEs commonly associated with regorafenib (fatigue, HFSR, hypertension, diarrhea) was generally lower in the dose-escalation group vs. the standard-dose group during both cycles. The most common grade 3/4 TEAEs (dose escalation vs. standard dose) were fatigue (13% vs. 18%), HFSR (15% vs. 16%), abdominal pain (17% vs. 6%), and hypertension (7% vs. 15%). Additionally, a prespecified analysis of cycle 1 showed that the rate of grade 2/3 HFSR was lower in the dose-escalation group vs. the standard-dose group (Bekaii-Saab et al., 2019b).

Secondary efficacy endpoints showed that the dose-escalation strategy did not negatively impact regorafenib activity; median PFS was 2.8 (dose escalation) vs. 2.0 (standard dose) months (HR, 0.84; log-rank p = .38). Median OS was numerically longer in the dose-escalation group (9.8 vs. 6.0 months; HR, 0.72; log-rank p = .12).

QUALITY OF LIFE

Quality of life was assessed by applicable instruments (HFSR-specific Hand–Foot Syndrome 14 [HFS-14]; Brief Fatigue Inventory [BFI]; Linear Analogue Self-Assessment [LASA]; Bretscher et al., 1999; Mendoza et al., 1999; Niska et al., 2017; Sibaud et al., 2011) at baseline and at the end of weeks 2, 4, 6, and 8 (Table 1; Bekaii-Saab et al., 2019b). At baseline, LASA and BFI scores were similar between the dosing strategies. At week 2, the mean BFI scores were significantly higher in the dose-escalation group for current fatigue, general activity interference, mood interference, walking ability interference, and normal work interference (Table 1). There were no significant differences between the dosing strategies at weeks 4, 6, and 8. Although overall scores on the HFS-14 and LASA questionnaires were slightly higher in the dose-escalation group, the differences were not significant. A sensitivity analysis, in which missing values were imputed to the worst possible value for the given measure, supported the QOL results (Bekaii-Saab et al., 2019b). Observed improvements in fatigue and other QOL scores at week 2 in the dose-escalation group vs. the standard-dose group suggest that the dose-escalation strategy may be advantageous when standard dosing appears to compromise QOL.

Application of clobetasol before the development of HFSR (pre-emptive use) during the first two cycles of regorafenib treatment significantly reduced the incidence of HFSR and was associated with better QOL compared with application of clobetasol after development of HFSR (reactive use; Jatoi et al., 2021). Over the first two cycles, no evidence of HFSR was observed in 30% of patients who received pre-emptive clobetasol (n = 61) vs. 13% of patients who received reactive clobetasol (n = 55, p = .03).

IMPLICATIONS FOR CLINICAL PRACTICE

The Oncologist's Perspective

Oncologists have been using regorafenib in clinical practice since 2012, and this experience has provided insights to help patients derive the maximum benefit from treatment. For example, in both interventional trials and real-world studies, the primary effect of regorafenib is exerted through disease stabilization (Ducreux et al., 2019; Grothey et al., 2013b; Li et al., 2015). Therefore, optimizing therapy requires maximizing treatment duration. Regorafenib-related AEs should be managed with a goal of keeping patients on treatment for as long as possible. ReDOS showed that a dose-escalation strategy in the first cycle allowed significantly more patients to remain on treatment through to cycle 3 compared with standard dosing (Bekaii-Saab et al., 2019b). The dose-escalation strategy was designed to minimize early AEs, to allow patients to reach the maximum tolerated dose within the first cycle, and to derive maximum treatment benefit. Oncologists can employ this strategy as

Table 1. Summary of Quality of Life Assessment Results from ReDOS

Treatment group	Dose escalation, [*n*[a]], mean score (95% CI)					Standard dose, [*n*[a]], mean score (95% CI)				
Week	**0**	**2**	**4**	**6**	**8**	**0**	**2**	**4**	**6**	**8**
HFS-14 score (2–100)	NA	[38] 19.7 (12.0, 27.4)	[31] 24.1 (14.9–33.3)	[28] 21.7 (13.5–29.9)	[28] 24.2 (16.7–31.7)	NA	[47] 23.0 (15.2–30.9)	[39] 16.3 (10.2–22.3)	[34] 19.7 (11.6–27.8)	[28] 17.6 (9.8–25.5)
LASA overall score (0–10)	[52] 7.6 (7.1–8.2)	[45] 7.1 (6.5–7.7)	[37] 7.1 (6.5–7.8)	[35] 7.5 (6.9–8.1)	[32] 7.4 (6.8–8.0)	[62] 7.8 (7.4–8.3)	[51] 6.3 (5.7–6.9)	[45] 7.2 (6.6–7.8)	[35] 7.1 (6.4–7.8)	[30] 7.0 (6.4–7.6)
BFI score (0–10)										
Current fatigue	[52] 6.1 (5.3–6.9)	[46] 5.3 (4.5–6.1)[b]	[38] 6.0 (5.2–6.8)	[35] 5.8 (4.8–6.7)	[33] 5.8 (4.8–6.8)	[61] 6.2 (5.6–6.8)	[52] 4.3 (3.6–5.0)[b]	[44] 5.6 (4.8–6.3)	[34] 5.1 (4.2–5.9)	[30] 5.5 (4.7–6.3)
Usual fatigue past 24 hours	[52] 6.2 (5.5–6.8)	[46] 5.0 (4.2–5.7)	[38] 6.1 (5.4–6.9)	[35] 5.5 (4.6–6.4)	[33] 5.9 (5.0–6.7)	[61] 6.2 (5.5–6.8)	[52] 4.5 (3.8–5.2)	[45] 5.6 (4.8–6.3)	[34] 5.2 (4.3–6.0)	[30] 5.3 (4.5–6.2)
Worst fatigue past 24 hours	[52] 5.5 (4.6–6.3)	[46] 4.4 (3.6–5.2)	[37] 5.2 (4.2–6.2)	[35] 4.7 (3.7–5.7)	[33] 5.2 (4.3–6.2)	[60] 5.4 (4.6–6.1)	[52] 3.8 (3.0–4.5)	[45] 5.2 (4.4–6.0)	[34] 4.4 (3.5–5.4)	[30] 4.8 (3.8–5.8)
General activity interference	[52] 6.4 (5.6–7.1)	[46] 5.6 (4.7–6.5)[b]	[37] 6.1 (5.3–7.0)	[35] 5.7 (4.7–6.6)	[33] 6.0 (4.9–7.1)	[61] 6.7 (6.0–7.4)	[52] 4.3 (3.5–5.1)[b]	[45] 5.8 (5.0–6.6)	[34] 5.3 (4.3–6.2)	[30] 5.8 (4.8–6.7)
Mood interference	[52] 6.8 (6.0–7.5)	[46] 6.2 (5.4–7.1)[b]	[37] 6.7 (6.0–7.5)	[35] 6.3 (5.4–7.2)	[33] 6.6 (5.6–7.7)	[61] 6.8 (6.2–7.5)	[52] 4.9 (4.1–5.8)[b]	[45] 6.3 (5.4–7.2)	[34] 6.0 (5.0–7.1)	[30] 6.3 (5.3–7.4)
Walking ability interference	[52] 6.6 (5.8–7.5)	[46] 6.0 (5.1–6.9)[b]	[37] 6.3 (5.4–7.2)	[35] 5.5 (4.5–6.5)	[33] 6.2 (5.2–7.3)	[61] 6.7 (6.0–7.5)	[52] 4.5 (3.7–5.3)[b]	[45] 5.9 (5.0–6.8)	[34] 5.6 (4.6–6.6)	[30] 5.9 (4.9–6.9)
Normal work interference	[52] 6.1 (5.3–6.9)	[46] 5.5 (4.6–6.4)[b]	[37] 6.1 (5.3–7.0)	[35] 5.4 (4.5–6.4)	[33] 6.2 (5.1–7.2)	[61] 6.5 (5.8–7.1)	[52] 4.2 (3.3–5.0)[b]	[45] 5.7 (4.9–6.6)	[34] 5.2 (4.2–6.2)	[30] 5.4 (4.4–6.4)
Relations interference	[52] 7.1 (6.3–7.8)	[46] 6.4 (5.5–7.3)	[37] 7.1 (6.3–7.9)	[35] 6.7 (5.8–7.7)	[33] 7.2 (6.2–8.1)	[61] 7.6 (6.8–8.2)	[52] 6.1 (5.3–6.9)	[45] 6.7 (5.7–7.6)	[34] 6.4 (5.4–7.4)	[30] 6.7 (5.7–7.8)
Enjoyment of life interference	[52] 6.3 (5.4–7.2)	[46] 5.9 (4.9–6.8)	[37] 6.7 (5.8–7.6)	[35] 5.8 (4.8–6.8)	[33] 6.8 (5.7–7.8)	[61] 6.8 (6.1–7.4)	[52] 5.0 (4.2–5.8)	[45] 6.0 (5.2–6.9)	[34] 5.6 (4.5–6.7)	[30] 6.2 (5.2–7.3)

Note. The HFSR-specific HFS-14 scale includes 14 questions with domains for hands, feet, and social impacts (Sibaud et al., 2011). The final score ranges from 2 to 100, with a higher score indicating a greater QOL impact (i.e., worse QOL; Sibaud et al., 2011). To facilitate comparison with other QOL assessments, the HSF-14 score was converted to a 0–100 scale, where a higher score indicates better QOL. The BFI is a nine-item questionnaire validated for the assessment of fatigue and fatigue-related impairment in patients with cancer (Mendoza et al., 1999). The BFI provides scores of 0–10 for current, usual, and worst fatigue (over the previous 24 hours) and for the degree to which fatigue has interfered with general activity, mood, walking ability, normal work, relationships, and enjoyment of life; higher scores indicate greater fatigue or a greater impact of fatigue (i.e., worse QOL; Mendoza et al., 1999). For consistency and to facilitate comparison with other assessments, the scale for the BFI score was converted, such that a higher score indicates a better QOL. A LASA questionnaire was used to measure elements of overall QOL (Bretscher et al., 1999). The LASA provides scores of 0–10 for 12 elements (including mental, physical, emotional, and spiritual wellbeing; pain; fatigue; and legal and financial concerns); higher scores indicate better QOL (Niska et al., 2017). BFI = Brief Fatigue Inventory; HFS-14 = Hand–Foot Syndrome 14; LASA = Linear Analogue Self-Assessment; NA = not applicable; QOL = quality of life.

[a]Number of patients with available assessments at each time point.

[b]Statistically significant difference between the dose-escalation and the standard-dose strategy at the indicated timepoint (t test or Wilcoxon rank sum, $p < .05$). All other comparisons were statistically non-significant.

some regorafenib-related AEs occur early and are noncumulative. This strategy cannot be used with traditional agents with cumulative toxicities (e.g., oxaliplatin- and irinotecan-based chemotherapy; Braun & Seymour, 2011; Kelly & Goldberg, 2005).

ReDOS enrolled "clinically fit" (ECOG PS 0–1), adult patients (aged ≥ 18 years) who had progressed on standard systemic treatments for mCRC (Bekaii-Saab et al., 2019b). For patients who are frailer than those included in clinical trials (i.e., ECOG PS > 1, presence of significant comorbidities and/or geriatric features, or those who have received multiple lines of prior systemic therapy for metastatic disease leading to cumulative toxicity), starting regorafenib below 160 mg/day might be a reasonable alternative to starting at the standard dose. The dose can then be escalated over the first 1–2 cycles to reach a target of 160 mg/day, if tolerated.

The Advanced Practice Provider's Perspective

Advanced practice registered nurses (APRNs) and physician assistants (collectively known as APPs in the United States), as well as registered nurses (RNs), are crucial to the interdisciplinary care of patients with cancer. Most APRNs are nurse practitioners; other APRNs practicing in oncology include certified registered nurse anesthetists and clinical nurse specialists (Nevidjon et al., 2010; Reynolds & McCoy, 2016).

Advanced practice providers are part of the interdisciplinary team developing a care plan, providing supportive care, patient monitoring, and therapeutic management (including drug-related AEs) with the active engagement and direction of oncologists. Advanced practice providers play vital roles in ensuring that patients and/or caregivers have a solid understanding of potential AEs related to oncology treatments and strategies for their management/mitigation. As regorafenib is an oral therapy, it is self-administered at home, which heightens the importance of patient education at the start of treatment and communication with patients between office visits. Patients with mCRC who are prescribed regorafenib have usually received two or more prior lines of systemic therapy; therefore, maintaining QOL becomes a key goal (Arnold et al., 2018; Bayer AG, 2023; Bayer HealthCare Pharmaceuticals, 2020). Providing APPs with education, including information on how to distinguish between the patient's disease trajectory and common regorafenib-related AEs, provides them with the knowledge to ensure that patients obtain the maximum benefit from this therapy through education and support. Advanced practice providers counsel patients to take regorafenib tablets at the same time each day. Ideally, the tablets are swallowed whole with water after a low-fat meal containing < 600 calories and < 30% fat (Bayer AG, 2023). A suitable low-fat meal that comprises 520 calories and 2 g of fat would include cereal (approximately 30 g), skimmed milk, a slice of toast with jam, a glass of apple juice, and a cup of coffee or tea (Bayer AG, 2023).

Adverse events commonly associated with regorafenib include HFSR, rash, oral mucositis, diarrhea, hypertension, abnormalities of liver enzymes, and fatigue (Table 2; Ducreux et al., 2019; Grothey et al., 2013b; Li et al., 2015; Van Cutsem et al., 2019; Yamaguchi et al., 2019). The most commonly observed AE is fatigue, which is one of the most distressing and activity-limiting symptoms that patients with cancer endure, especially during the final disease stages, and can have a significant impact on QOL (De Wit et al., 2014; Hofman et al., 2007). Regorafenib-related fatigue can be difficult to manage and is often difficult to distinguish from general fatigue related to the disease and/or previous treatments. One of the recommended strategies to combat fatigue is encouraging physical activity (De Wit et al., 2014). Prior to treatment, the patient's level of activity can be assessed using the BFI, which should be monitored weekly during the first two cycles and twice monthly thereafter (Hofheinz et al., 2015; Mendoza et al., 1999). Additionally, documenting fatigue-related symptoms daily using a patient-recorded diary allows APPs to continually track and advise patients on effective management/mitigation strategies.

In our experience, a substantial subset of patients are prescribed regorafenib using the first-cycle dose-escalation strategy defined in ReDOS (Bekaii-Saab et al., 2019b). The advantages of using this strategy include fewer and/or less severe AEs, predictability in the onset of any TEAEs, better treatment adherence, and improved patient QOL/wellbeing, all of which increase the likelihood of patients remaining on treatment for longer, thus improving outcomes (Bekaii-Saab et al., 2019b).

Table 2. Management Strategies for Regorafenib-Related Adverse Events

Adverse event	Description	Timing of onset	Management strategies
HFSR (palmar plantar erythrodysesthesia syndrome)	• Localized hyperkeratotic lesions (may be surrounded by erythematous regions) • Areas of skin under the most pressure or flexure most likely affected (i.e., palms of the hands, fingertips, finger webs, distal phalanges, soles of feet, toes)	• Within 2–4 weeks of initiation	• Detect early and treat promptly to reduce severity and duration • Perform a full-body examination before treatment • Assess QOL with a validated tool • Soften and/or remove calluses with keratolytic creams (e.g., 10%–40% urea or 5%–10% salicylic acid) • Monitor weekly during cycles 1 and 2, then every 4–6 weeks thereafter • Counsel patient to avoid pressure/friction on skin, or any traumatic activity • Protect pressure points on the feet with cotton socks and well-padded/fitted shoes • Counsel patient to wear padded gloves when doing strenuous activities involving the hands • Apply creams and moisturizers to hydrate the skin; avoid hot water and alcohol-based soaps and sanitizers to prevent dehydration • Cool the skin with cold packs • Recommend topical local anesthetics to relieve pain • Consider regorafenib dose modifications if symptoms persist despite active management
Rash or desquamation (maculopapular rash)	• Macules (flat, discolored areas of skin) and papules (solid elevations of skin) • Symptoms include photosensitivity, erythema, dry or peeling skin, blistering, and pruritus	• Predominantly occurs within the first treatment cycle, and the incidence is considerably reduced in subsequent cycles	• Monitor for rash weekly during cycles 1 and 2, then every 4 weeks thereafter • Use non-alcohol-based emollients and mild soaps, and avoid exposure to extreme temperatures and/or sunlight • Treat grade 2 or 3 symptoms with topical corticosteroids (e.g., clobetasol propionate 0.05%); avoid systemic steroids • Consider referral to a dermatologist

Note. ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; HCP = healthcare professional; HFSR = hand–foot skin reaction; QOL = quality of life; ULN = upper limit of normal. Information from De Wit et al. (2014); McLellan et al. (2015).

[a]Graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Diarrhea: grade 1, < 4 per day + mild increase in ostomy output; grade 2, 4–6 stools per day + moderate ostomy output; grade 3, ≥ 7 stools per day + severe ostomy output, incontinence, hospitalization indicated, limiting self-care ADL; grade 4, life-threatening consequences, urgent intervention needed; grade 5, death. Hypertension: grade 1, prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg); grade 2, stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits; grade 3, stage 2 hypertension (systolic BP > 160 mmHg or diastolic BP ≥ 100 mmHg); grade 4, life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, or hypertensive crisis); grade 5, death. Fatigue: grade 1, relieved by rest; grade 2, not relieved by rest; limiting instrumental ADL; grade 3, not relieved by rest; limiting self-care ADL.

Table 2. Management Strategies for Regorafenib-Related Adverse Events (cont.)

Adverse event	Description	Timing of onset	Management strategies
Stomatitis (oral mucositis)	• Inflammation of the mucous membranes lining the mouth and oropharynx	• Usually 5–14 days after the start of a treatment cycle • May occur only in cycle 1, or may be recurrent	• Practice good oral hygiene • Use fluoride toothpaste and a soft toothbrush or swab after meals and before sleep • Rinse mouth regularly with an alcohol-free mouthwash, saline, or bicarbonate solution • Clean dentures daily • Avoid hot or spicy beverages and food • If stomatitis occurs, increase the frequency of rinsing with mouthwash (every 1–2 hours); advise patients to use a local anesthetic, such as viscous lidocaine, before rinsing if mouthwashes are painful • Consider use of nystatin, hexetidine, mepivacaine hydrochloride, and bicarbonate • Recommend a course of antifungal treatment (e.g., nystatin) for suspected fungal throat infections • Assess oral intake of food and drink (pain, dry mouth, and difficulty swallowing may interfere with intake) • Consider use of analgesics if severe • Consider regorafenib dose modifications if severe or recurrent
Diarrhea	• Increased number of stools per day and increased ostomy output over baseline[a]	• Upon treatment initiation	• Provide dietary advice to minimize the likelihood of diarrhea (e.g., ensuring a low intake of fiber) before initiating treatment • Counsel patients to contact their HCP if they experience an increase of more than three stools per day • Counsel patients on the variation in stool form: changes in stool number or consistency do not always require treatment • Grade 1 or 2 diarrhea: recommend loperamide (two 2-mg tablets) after the first stool, then one tablet every 2 hours, until 12 hours after the last watery stool for a maximum of 48 hours • Uncontrolled diarrhea (e.g., grade ≥ 3 after 48 hours of loperamide treatment): counsel patients to increase fluid intake, and consider hospital admission

Note. ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; HCP = healthcare professional; HFSR = hand–foot skin reaction; QOL = quality of life; ULN = upper limit of normal. Information from De Wit et al. (2014); McLellan et al. (2015).

[a]Graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Diarrhea: grade 1, < 4 per day + mild increase in ostomy output; grade 2, 4–6 stools per day + moderate ostomy output; grade 3, ≥ 7 stools per day + severe ostomy output, incontinence, hospitalization indicated, limiting self-care ADL; grade 4, life-threatening consequences, urgent intervention needed; grade 5, death. Hypertension: grade 1, prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg); grade 2, stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits; grade 3, stage 2 hypertension (systolic BP > 160 mmHg or diastolic BP ≥ 100 mmHg); grade 4, life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, or hypertensive crisis); grade 5, death. Fatigue: grade 1, relieved by rest; grade 2, not relieved by rest; limiting instrumental ADL; grade 3, not relieved by rest; limiting self-care ADL.

Table 2. Management Strategies for Regorafenib-Related Adverse Events (cont.)

Adverse event	Description	Timing of onset	Management strategies
Hypertension	• Elevated BP[a]	• During treatment (effects are not cumulative) • After discontinuation of regorafenib, BP decreases to pretreatment levels	• Check BP at baseline; treat if elevated • Monitor weekly during cycles 1 and 2; treat if elevated • Counsel patients to measure and record their BP at home each day (to detect "white coat syndrome") • Treat BP exceeding 140/90 mmHg (grade 2) with antihypertensive medication • Avoid use of diuretics due to an increased risk of diarrhea
Liver abnormalities	• Indicative of liver toxicity • Yellow discoloration of the skin and whites of the eyes, nausea and vomiting, very dark urine, and changes in sleep patterns	• Soon after treatment initiation	• Monitor AST, ALT, and bilirubin levels every 2 weeks during cycles 1 and 2 • AST or ALT > 5 × ULN: interrupt regorafenib, consider restarting when transaminases are < 3 × ULN or return to baseline • AST or ALT > 20 × ULN, or AST or ALT > 3 × ULN and bilirubin > 2 × ULN: discontinue regorafenib • Patients with Gilbert's syndrome have high baseline levels of bilirubin; if bilirubin levels are elevated, follow the advice for elevated liver enzymes—elevated transaminases need not be taken into consideration
Fatigue	• Generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities[a]	• Upon treatment initiation	• Monitor weekly during cycles 1 and 2, then every 2 weeks thereafter • Counsel patients to contact their healthcare team if fatigue develops or worsens between visits • If drug-related fatigue occurs, recommend daily rest and time to recuperate • Encourage patients to exercise • Consider regorafenib dose modifications for grade 3 fatigue

Note. ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; HCP = healthcare professional; HFSR = hand–foot skin reaction; QOL = quality of life; ULN = upper limit of normal. Information from De Wit et al. (2014); McLellan et al. (2015).

[a]Graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Diarrhea: grade 1, < 4 per day + mild increase in ostomy output; grade 2, 4–6 stools per day + moderate ostomy output; grade 3, ≥ 7 stools per day + severe ostomy output, incontinence, hospitalization indicated, limiting self-care ADL; grade 4, life-threatening consequences, urgent intervention needed; grade 5, death. Hypertension: grade 1, prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg); grade 2, stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits; grade 3, stage 2 hypertension (systolic BP > 160 mmHg or diastolic BP ≥ 100 mmHg); grade 4, life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, or hypertensive crisis); grade 5, death. Fatigue: grade 1, relieved by rest; grade 2, not relieved by rest; limiting instrumental ADL; grade 3, not relieved by rest; limiting self-care ADL.

The Pharmacist's Perspective

The role of oncology pharmacists has evolved in recent decades, extending beyond dispensing to provide direct evidence-based care (Hematology/Oncology Pharmacy Association, 2024; Holle et al., 2020). Clinical pharmacists who are integrated within the MDT (typically board-certified oncology pharmacists) are usually responsible for providing in-person initial education to both the patient and caregiver, ensuring that prescriptions are sent to the appropriate pharmacy in a timely manner, obtaining prior authorization and addressing insurance issues and/or copay assistance, closely monitoring the patient for treatment-related AEs, and either recommending or implementing dose adjustments. Pharmacists who practice in this capacity develop pharmaceutical care plans, which include treatment strategies and supportive care management, such as recommending and/or prescribing symptom-relieving treatments.

Patient education prior to starting and communication during therapy are key roles of the pharmacist and are important for patients receiving oral treatments, such as regorafenib. Prior to treatment, pharmacists provide patients with the necessary resources, including online information regarding their treatment (see *Resources for Patients*). Patients are advised how to use treatment calendars, pill boxes, and treatment kits. Additionally, the pharmacist explains the dosing schedule and educates the patient on how to manage TEAEs, both proactively and during therapy. The patient is counseled to use moisturizers, and address hyperkeratoses and calluses before initiating treatment to minimize the risk of developing HFSR. The pharmacist also explains how the patient should report TEAEs, either to the pharmacist or an APP. When a patient reports an AE that may require a dose modification, the physician or APP is notified, and a decision is taken within the team. A new prescription request is sent electronically to the pharmacist for patient collection. The pharmacist may provide advice by e-mail or telephone to assist with any prescription-related enquiries. Depending on their level of responsibility, the pharmacist may even be involved at the forefront of clinical decision-making, including adjusting dose schedules, which are always communicated beforehand with the patient. The pharmacist is also responsible for managing the patients' expectations related to drug supply, and for notifying them of any potential delays arising from mail order pharmacy protocols and insurance approvals.

Clinics that do not have clinical pharmacists rely on the dispensing pharmacist to ensure that the patient has an uninterrupted supply of medication at the correct dose and schedule. Good communication between the pharmacist and the patient and/or caregiver is crucial to ensure that the dose-adjustment strategy is understood. Managing the supply of regorafenib tablets is a challenge, whether an oncologist prescribes regorafenib at the standard dose or uses the ReDOS dose-escalation strategy in cycle 1. With standard dosing, the prescriber reactively adjusts the dose after the patient experiences AEs. When the dose is reduced, there is a discrepancy between the quantity of tablets needed to complete the cycle and the quantity in the patient's possession. This can lead to confusion, may result in dosing errors, and can affect patient safety. Patient education is important to ensure that the patient understands the revised dosing schedule and is not surprised to have extra tablets at the end of the cycle.

Alternatively, with the ReDOS dose-escalation strategy, the dose may change weekly during cycle 1. To minimize confusion and dosing errors, the prescription should clearly describe the first-cycle dose-escalation strategy so that any dose adjustments are clear for the pharmacist, patient, and payer. Ambiguity in the prescription may cause delays in dispensing and result in treatment interruptions, especially if the prescriber and/or payer must be contacted by the pharmacist. The time required to obtain clarification from the prescriber and seek approval from the patient's insurance provider can cause prescription delays. To avoid such delays, a comprehensive written instruction and/or a calendar indicating the time of planned dose escalations should be included in the prescription and provided to the patient.

RESOURCES

Resources for Health-Care Professionals

Advanced practice providers and pharmacists who are informed about strategies available to

manage regorafenib-related AEs are best positioned to assist their patients. Suitable resources include journal articles providing information related to the prevention and management of AEs, including regorafenib-related HFSR, for example the article on the prevention and management of adverse events related to regorafenib (De Wit et al., 2014; McLellan et al., 2015) and websites of organizations such as the National Community Oncology Dispensing Association (NCODA; National Community Oncology Dispensing Association, 2021) and the Hematology/Oncology Pharmacy Association (HOPA; Hematology/Oncology Pharmacy Association, 2024), which include information for pharmacists on monitoring patients receiving regorafenib.

Resources for Patients

Patient education is crucial for patients to benefit from regorafenib. During a consultation, patients are informed about its mechanism of action and route of administration. Educating the patient about common AEs prior to therapy, along with how they can be effectively managed, is important with respect to compliance and, consequently, clinical outcomes. Additionally, APPs and pharmacists advise patients to inform their assigned healthcare team upon the onset of any symptoms, as early detection can prevent symptoms from worsening. Several resources are available for patients. APPs or pharmacists can provide patients with a regorafenib starter kit that contains a patient brochure with information about how regorafenib works, how it should be administered, managing common AEs, and services available to assist with the cost of treatment; a caregiver brochure with information on regorafenib and strategies for caring for patients and for themselves; a digital thermometer; and pill boxes for organizing regorafenib tablets for each cycle. Health-care providers are encouraged to distribute free patient education sheets (PES), developed by the NCODA and its partners, which contain easy-to-understand information about oral cancer drugs, including regorafenib, and to refer patients to the PES website (Patient Education Sheets [Formerly IVE and OCE Sheets], 2025). A universally accessible website is available to assist patients with meal planning (U.S. Department of Agriculture, 2020).

CONCLUSION

The ReDOS trial provides an evidence-based guide for health-care professionals to optimize regorafenib dosing in patients with mCRC, without compromising outcomes. The dose-escalation strategy improved tolerability and QOL parameters that included fatigue and activity/mood interference during the first two cycles of treatment, without reducing overall drug exposure, vs. standard regorafenib dosing. In our experience, the advantages of using a dose-escalation approach with regorafenib include better management of associated AEs and improved patient adherence, which helps patients to stay on treatment and improves outcomes. Furthermore, the ReDOS dose-escalation strategy may be a valid dose-optimization approach for frail patients, in whom tolerability and QOL is paramount. Patient education and support provided by APPs and pharmacists is vital to ensure continuity of care and that patients with mCRC derive the maximum benefit from treatment.

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