Case Study Series

Cases in the Management of Metastatic Colorectal Cancer: Use of Regorafenib as a Bridge to Chemotherapy

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Case 2 of a 3-Part Series

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Patient Case

The patient is a 62-year-old man with a long history of metastatic colorectal cancer (mCRC). His primary tumor was originally in the sigmoid colon, and he was found to have synchronous liver metastases at diagnosis (Table 1). His disease was *KRAS* and *BRAF* wild-type, human epidermal growth factor receptor 2 (HER2)-negative, and microsatellite stable.

Computed tomography (CT) imaging revealed oligometastatic disease in his liver. After consultation with a surgical oncologist, it was decided that the patient had potentially resectable mCRC. Thus, he initiated neoadjuvant therapy with capecitabine plus oxaliplatin (CAPEOX) and bevacizumab. Following 6 cycles of therapy, he underwent reevaluation and was found to have significant regression of his disease. We decided to pause systemic therapy. The patient underwent resection of his primary sigmoid tumor, as well as 3 liver lesions. Following this procedure, the patient was considered to have no evidence of disease. Because of his ultimately high risk of relapse, the patient was restarted on a low-dose mainte-

nance regimen with CAPEOX plus bevacizumab. After 9 months, his serum carcinoembryonic antigen (CEA) level began to rise. On repeat imaging, he began to show minor disease progression, with multiple small volume lung and liver lesions. Otherwise, he had an excellent performance status.

During a discussion with the patient, we conveyed that his disease was not resectable owing to the metastatic burden. The patient was focused on maintaining his ability to work full-time, which had been difficult during his first-line treatment course owing to the multiple infusions necessary. Based on this discussion, we decided to use regorafenib as a type of second maintenance therapy, with the goal of achieving stable disease. The patient agreed with this approach. The goal was to save systemic chemotherapy for a later time, when the tumor was more bulky and a response was needed.

The patient initiated treatment with regorafenib. We followed the dose-escalation strategy described in the ReDOS trial of 2 pills, followed by 3 pills, followed by 4 pills.[1] Ultimately, the patient reached a final dose of 120 mg daily. He tolerated this dose fairly well, with minimal

hand-foot syndrome, no liver function abnormalities, and mild fatigue. Blood work showed that his CEA level decreased slightly, and positron emission tomography/CT confirmed no new lesions. The patient was maintained on regorafenib for approximately 8 months before he developed signs of progressive disease. At this point, his disease progression became symptomatic, with more significant abdominal pain.

As a result, the patient began third-line treatment with folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus panitumumab. He developed a partial response, which lasted for 5 months. Following disease progression, he began fourth-line treatment with irinotecan plus panitumumab.

Rationale for the Treatment Decisions

Neoadjuvant Chemotherapy and Surgical Resection Followed by Maintenance Chemotherapy

In general, patients with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation to assess resectability. During this evaluation, consideration is given to the likelihood of achieving complete resection of all visible disease with negative surgical margins, while maintaining adequate liver reserve. Resection should not be performed unless complete removal of all known tumor tissue is a realistic outcome (R0 resection).[2]

Maintenance therapy with capecitabine plus bevacizumab became a standard of care following the CAIRO3 study, an open-label, randomized phase 3 trial that compared this combination vs observation alone in patients with mCRC who had achieved stable disease or better following first-line treatment with CAPEOX plus bevacizumab.[3] Maintenance treatment with capecitabine plus bevacizumab significantly prolonged the median first progression-free survival compared with observation (8.5 months vs 4.1 months; P<.0001; adjusted hazard ratio [HR], 0.39; 95% CI, 0.33-0.48). After first progression, patients in both the maintenance and observation arms received CAPEOX plus bevacizumab again until second progression. The primary endpoint, the median second progression-free survival, was 11.7 months in the maintenance arm vs 8.5 months in the observation arm (HR, 0.67; 95% CI, 0.56-0.81; P<.0001). A total of 54% of patients overall received CAPEOX/bevacizumab after the first progression. A nonsignificant trend toward improved overall survival was observed with maintenance therapy compared with observation alone (21.6 months vs 18.1 months; adjusted HR, 0.83; 95% CI, 0.68-1.01; P=.06). Overall, the maintenance regimen was well tolerated, with no effect on quality of life, although patients experienced a higher incidence of hand-foot syndrome (23%).

Table 1. Key Points of the Case

Initial Clinical Presentation
• 62-year-old man with a long history of metastatic colorectal cancer
• The primary tumor was originally in the sigmoid colon
• Synchronous liver metastases were identified at diagnosis

Pathology
• *KRAS* wild-type
• *BRAF* wild-type
• HER2-negative
• Microsatellite stable

Disease Characteristics
• Oligometastatic disease in the liver

Primary Treatment
• Neoadjuvant therapy with CAPEOX and bevacizumab
• Resection of the primary sigmoid tumor and 3 liver lesions

Lines of Therapy for Metastatic Disease
• Low-dose maintenance regimen with capecitabine plus bevacizumab
• Regorafenib
• FOLFIRI plus panitumumab

CAPEOX, capecitabine plus oxaliplatin; FOLFIRI, folinic acid, fluorouracil, and irinotecan; HER2, human epidermal growth factor receptor 2.

Dose-Escalated Regorafenib in the Second-Line Setting

Upon disease progression after first-line therapy, the patient had an excellent performance status and was experiencing minimal symptom burden. Thus, the patient did not require a rapid reduction in tumor volume, and stable disease was an acceptable outcome. In this case, regorafenib was initiated as a second-line treatment to act as a nonchemotherapy bridge following a relatively cytotoxic first-line treatment. As an oral formulation, regorafenib can be administered at home, which also accommodated the patient's desire to continue working.

In mCRC, the US Food and Drug Administration has approved regorafenib for the third-line treatment of patients who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti–vascular endothelial growth factor (VEGF) therapy; and an anti–epidermal growth factor receptor (EGFR) therapy (if *RAS* wild-type).[4] This approval was based on the results of the CORRECT pivotal trial, as well as the confirmatory CONCUR trial.[5,6] Both studies demonstrated an overall survival benefit with regorafenib compared with placebo in this setting, which was largely attributed to durable stable disease rather than tumor response. For example, in the CORRECT trial, the objective response rate was 1.0% with regorafenib and 0.4% with placebo
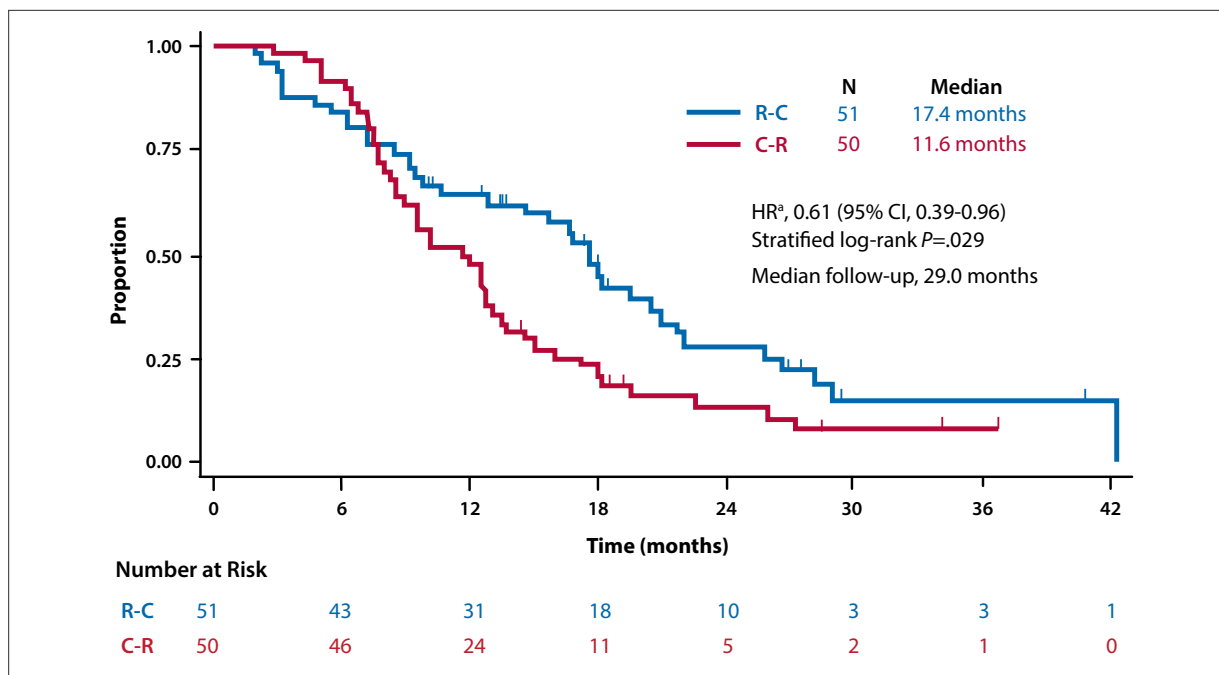
Figure 1. Overall survival in the REVERCE trial. This phase 2 study compared the sequence of regorafenib followed by cetuximab (R-C) vs the sequence of cetuximab followed by regorafenib (C-R). [a]Adjusted by intention to use irinotecan. HR, hazard ratio. Adapted from Shitara K et al. *Ann Oncol.* 2019;30(2):259-265.[8]

(*P*=.19).[5] All of the responses were partial. However, the disease control rate (patients who achieved either a partial response or stable disease), was much higher: 41% with regorafenib vs 15% with placebo (*P*<.0001).

In the CONCUR trial, prior treatment with the targeted biologic therapies bevacizumab, cetuximab, or panitumumab was allowed but not mandatory.[6] Indeed, 41% and 38% of patients in the regorafenib and placebo arms, respectively, had not received any of these targeted therapies at baseline. In an exploratory analysis, the benefits of regorafenib were stronger among patients who were naive to one of these targeted therapies (HR, 0.31; 95% CI, 0.19-0.53) than among patients who had prior exposure to a targeted therapy (HR, 0.78; 95% CI, 0.51-1.19).[6] These data support the earlier use of regorafenib in patients with mCRC, as do results from a single-arm phase 2 study of first-line regorafenib monotherapy in frail or unfit patients unable to tolerate combination cytotoxic agents.[7]

Clinical trials have begun to explore regorafenib treatment in alternative mCRC settings, such as earlier lines of therapy. REVERCE was an open-label, randomized, phase 2 clinical trial designed to assess the efficacy and safety benefit associated with the treatment sequence of regorafenib followed by cetuximab, compared with cetuximab followed by regorafenib, among patients with

previously treated mCRC.[8] To be eligible for enrollment in the REVERCE study, patients had to have histopathologically proven unresectable metastatic or locally advanced colorectal adenocarcinoma. Patients had an inadequate response to prior therapy with fluoropyrimidines, oxaliplatin, and irinotecan, but were naive to treatment with an anti-EGFR antibody. All patients were *KRAS* wild-type. They could have measurable or nonmeasurable disease. Their Eastern Cooperative Oncology Group (ECOG) performance status was 0 through 2, with adequate organ function.

In REVERCE, patients were randomly assigned to receive either sequential treatment with regorafenib followed by cetuximab with or without irinotecan (the R-C experimental arm), or sequential treatment with cetuximab with or without irinotecan followed by regorafenib (the C-R control arm).[8] In both arms, regorafenib was administered at a dose of 160 mg orally once daily for 3 weeks on and 1 week off. Both sequential treatment regimens were continued until disease progression, unacceptable toxicity, or patient withdrawal of consent. In both arms, the sequential treatment was then started between 7 and 28 days after completion of the first treatment. Randomization was stratified by study site, history of treatment with bevacizumab, and intention to use irinotecan with cetuximab at the time of study enrollment.
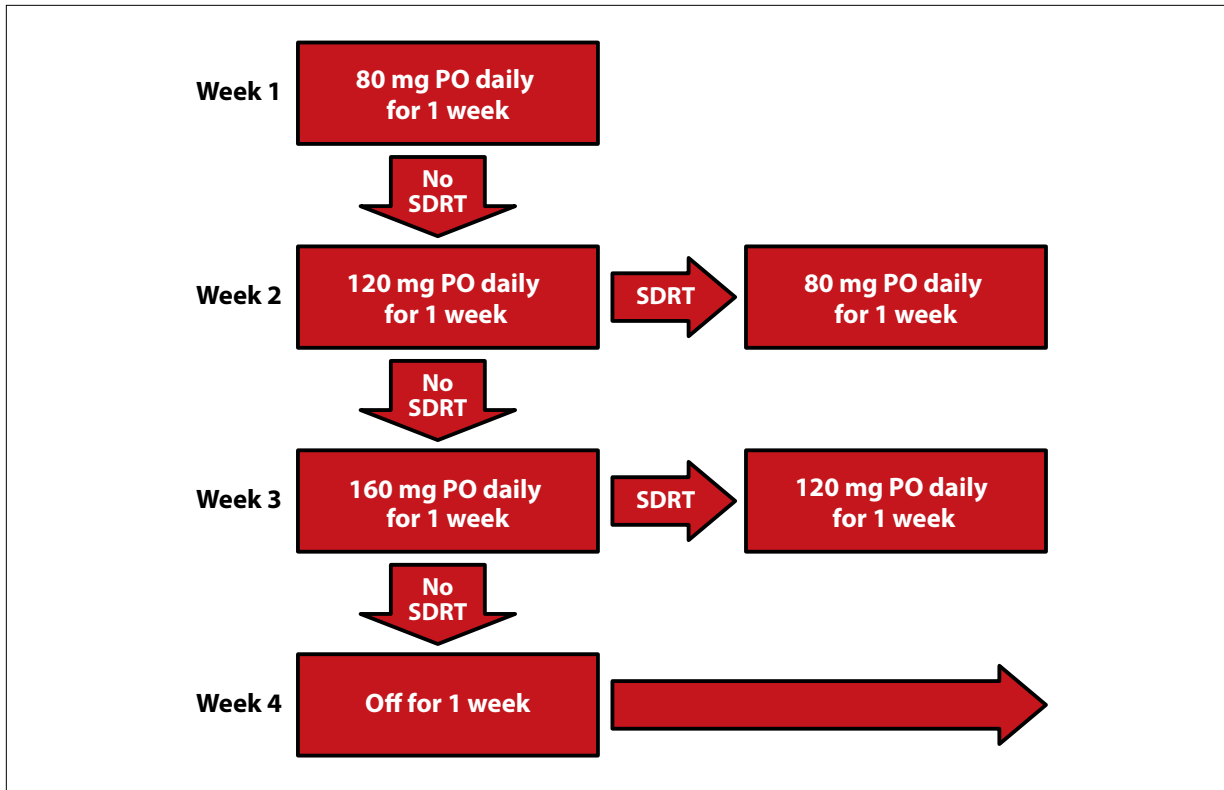
Figure 2. Administration of regorafenib in a dose-escalated strategy can decrease toxicities. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2015;13(8):514-517.[12]

An intention to use irinotecan was reported in 59% of patients in the R-C arm and 64% in the C-R arm; the actual use was 49% and 64%, respectively.

The REVERCE trial randomly assigned 101 patients to treatment between November 2013 and September 2016.[8] Study enrollment was subsequently discontinued after slow accrual and changes in funding. Characteristics at baseline were not significantly different between the 2 treatment arms. Most patients were male (61% in the R-C arm and 66% in the C-R arm), and most had an ECOG performance status of 0 (67% and 78%). Left-sided disease was predominant (75% and 86%). The rates of metastasis in particular sites were as follows: liver (63% and 62%), lung (59% and 46%), lymph node (41% and 48%), and peritoneum (22% and 18%).

Adverse events led to a reduction in the dose of regorafenib in 65% of patients in the R-C arm and 38% of patients in the C-R arm.[8] The duration of regorafenib treatment was longer in the R-C arm vs the C-R arm.

The primary endpoint of the REVERCE study, overall survival, was improved with the R-C sequence. The median overall survival was 17.4 months in the R-C arm vs 11.6 months in the C-R arm (HR, 0.61; 95% CI, 0.39-0.96; stratified log-rank P=.0293; Figure 1).[8] The median

time to treatment failure of the sequential treatment, a secondary endpoint, was 7.4 months in the R-C arm vs 6.1 months in the C-R arm (HR, 0.60; 95% CI, 0.39-0.92; P=.017). The progression-free survival associated with the first treatment in each sequence (PFS1) was not significantly different between the 2 arms (2.4 months with R-C and 4.2 months with C-R; HR, 0.97; 95% CI, 0.62-1.54; P=.91). In contrast, the progression-free survival of the second treatment in each sequence (PFS2) was significantly prolonged in the R-C vs C-R arm (5.2 months vs 1.8 months; HR, 0.29; 95% CI, 0.17-0.50; P<.0001). The overall median progression-free survival for each arm was 9.0 months with R-C and 7.1 months with C-R (HR, 0.55; 95% CI, 0.34-0.90; P=.015).

Among patients with measurable disease in the R-C arm, treatment with regorafenib was associated with an objective response rate of 4% and a disease control rate of 46%.[8] This finding was in line with the low rates of response and high rates of disease stability in the COR-RECT and CONCUR trials.[5,6] In the C-R arm, there was a 20% rate of objective response and a 78% rate of disease control with cetuximab. In the R-C arm, treatment with cetuximab led to an objective response rate of 28% and a disease control rate of 77%. In the C-R arm, regorafenib
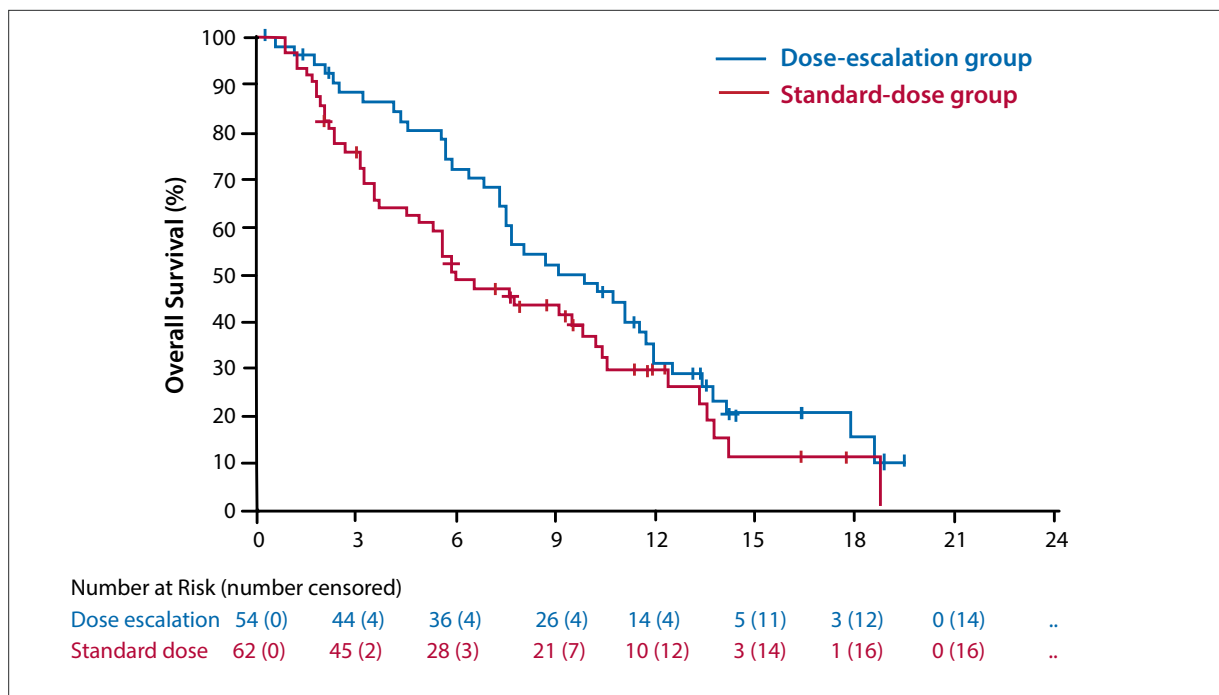
Figure 3. Overall survival in the randomized phase 2 ReDOS trial. In the dose-escalated arm, regorafenib was initiated at 80 mg/day, and then increased weekly up to 160 mg/day in the absence of significant drug-related toxicities. In the standard-dose arm, patients received regorafenib at 160 mg/day. Adapted from Bekaii-Saab TS et al. *Lancet Oncol.* 2019;20(8):1070-1082.[1]

was associated with an objective response rate of 0% and a disease control rate of 31%. The trends of low rates of response and higher rates of disease stability observed with regorafenib in both arms were similar to those observed in the CORRECT and CONCUR trials.[5,6]

In the REVERCE study, the rate of grade 3 or higher nonhematologic adverse events was 71% with regorafenib and 57% with cetuximab in the R-C arm, and 50% with cetuximab in the C-R arm and 63% with regorafenib in the C-R arm.[8] No new or unexpected adverse events were reported. Quality of life, assessed with the validated Japanese version of the EuroQol 5 Dimension (EQ-5D) questionnaire, did not significantly differ between the 2 arms (the difference in EQ-5D during all treatment periods was –0.011; *P*=.65).

Another important point regarding this patient's case was that regorafenib was administered using a dose-escalation strategy (Figure 2). The standard dosing regimen of regorafenib—160 mg once daily—was associated with a relatively high rate of toxicities (such as fatigue, hand-foot skin reaction, hypertension, and diarrhea) in the CORRECT and CONCUR studies.[5,6] Thus, the randomized phase 2 ReDOS trial evaluated an alternative dosing strategy in which regorafenib was initiated at a dose of 80 mg once daily on days 1 to 7.[1] In the absence of any significant drug-related toxicities, the dose of regorafenib

was then escalated to 120 mg once daily on days 8 to 14, then to 160 mg once daily on days 15 to 21. In cycle 2 and thereafter, patients subsequently received the highest tolerated dose from cycle 1. This alternative-dosing strategy was compared with the standard-dosing strategy.

Among 116 evaluable patients, the proportion of evaluable patients initiating cycle 3 (the primary endpoint) was 43% in the dose-escalated arm vs 26% in the standard-dosing arm (*P*=.043).[1] The median overall survival was 9.8 months in the dose-escalated arm and 6.0 months in the standard-dosing arm, but this difference did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank *P*=.12; Figure 3). Progression-free survival was similar between the 2 arms (HR, 0.84; 95% CI, 0.57-1.24; log-rank *P*=.38).

The rates of grade 3 adverse events frequently associated with regorafenib, including fatigue, hand-foot skin reaction, hypertension, and diarrhea, were lower in the dose-escalation group compared with the standard-dose group during the first 2 cycles of treatment.[1] The most common grade 3/4 adverse events reported were fatigue (13% in the dose-escalation arm vs 18% in the standard-dose arm), abdominal pain (17% vs 6%), hand-foot skin reaction (15% vs 16%), and hypertension (7% vs 15%).

At baseline, quality-of-life scores were similar between the 2 dosing arms at baseline.[1] By the second

week of treatment, the mean quality-of-life scores (per the Brief Fatigue Inventory questionnaire) were significantly better in the dose-escalation arm compared with the standard-dose arm across multiple measurements, including current fatigue, general activity interference, mood interference, walking ability interference, and normal work interference. However, the quality-of-life scores did not significantly differ at weeks 4, 6, and 8. The results from the ReDOS trial led a National Comprehensive Cancer Network panel to agree that a dose-escalation strategy is an appropriate alternative approach for regorafenib dosing.[2]

FOLFIRI Plus Panitumumab

This case study incorporated the use of FOLFIRI plus panitumumab in the third line of treatment, which was the second-line of chemotherapy owing to the use of regorafenib as a bridging regimen. The addition of panitumumab to FOLFIRI chemotherapy as second-line treatment for mCRC was established in a global, open-label, phase 3 trial.[9] This trial enrolled all-comers, but patients were evaluated according to *KRAS* status. A total of 597 patients were identified with *KRAS* wild-type disease. The median progression-free survival was 5.9 months with FOLFIRI plus panitumumab vs 3.9 months with FOLFIRI alone in this subpopulation (HR, 0.73; 95% CI, 0.59-0.90; *P*=.004). Although the median overall survival was numerically longer with the combination arm in patients with *KRAS* wild-type disease, this difference did not reach statistical significance. The median overall survival was 14.5 months with panitumumab plus FOLFIRI vs 12.5 months with FOLFIRI alone (HR, 0.85; 95% CI, 0.70-1.04; *P*=.12). Among patients with *KRAS* wild-type disease, the objective response rate was 35% in the panitumumab-plus-FOLFIRI arm vs 10% in the FOLFIRI arm (descriptive *P*<.001). The observed grade 3 and 4 adverse events were as expected, and included a higher rate of grade 3/4 skin toxicity with panitumumab plus FOLFIRI vs FOLFIRI alone (37% vs 2%, respectively).

Irinotecan Plus Panitumumab

After this patient experienced disease progression with panitumumab plus FOLFIRI, one option may have been to initiate trifluridine/tipiracil. However, this patient was exhibiting symptomatic metastases that required a rapid decrease in tumor volume. Like regorafenib, the response rate with trifluridine plus tipiracil in the pivotal RECOURSE study was low, and the treatment was

instead associated with disease stability.[10] Therefore, in this patient, a salvage regimen of irinotecan plus panitumumab was chosen. The use of this salvage regimen is supported by a single-arm, open-label phase 2 Spanish study that reported an objective response rate of 15.2% (all partial responses) and a median progression-free survival of 3.8 months (95% CI, 2.7-4.3) in *KRAS* wild-type patients. Diarrhea and rash were the most frequently reported grade 3 or 4 adverse events, as was expected with this regimen.[11]

Disclosure

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