Case Study Series

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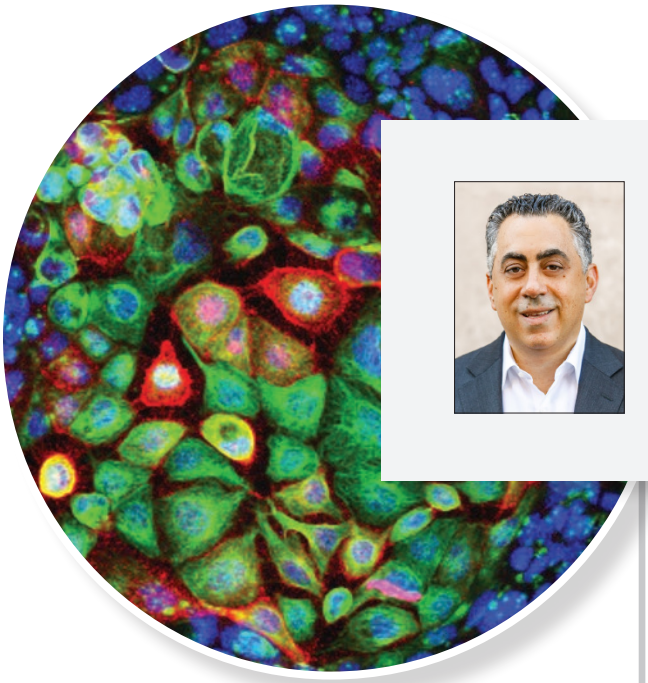
Cases in the Management of Metastatic Colorectal Cancer: Regorafenib as Second-Line Therapy After FOLFOXIRI Plus Bevacizumab in a Patient With a *KRAS* Mutation



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Regorafenib as Second-Line Therapy After FOLFOXIRI Plus Bevacizumab in a Patient With a *KRAS* Mutation

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Patient Case

A 53-year-old woman presented to her gastroenterologist with symptoms of bowel obstruction and right upper quadrant pain. A complete blood count indicated anemia (hemoglobin, 10.1 g/dL), and liver function tests showed elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The patient immediately underwent a colonoscopy, which revealed an ascending colon mass with near complete obstruction. A diverting ostomy was performed to help relieve the obstruction. A port was placed during her hospitalization.

Biopsy specimens confirmed right-sided adenocarcinoma of the colon. A follow-up computed tomography (CT) scan of the chest and pelvis showed evidence of multiple liver metastases, as well as several positive retrograde peritoneal lymph nodes. Next-generation sequencing of the biopsy samples indicated that the tumor was microsatellite stable (MSS), *BRAF* V600E wild-type, *NRAS* wild-type, and *HER2*-nonamplified. However, the tumor had a *KRAS* G13D mutation. At this point, the patient's carcinoembryonic antigen (CEA) level was 35 U/mL.

After recovering from surgery, the patient was referred to the specialty gastrointestinal oncology clinic. Based on her age and excellent performance status, the patient was a candidate for aggressive treatment. In consultation with her oncologist, the patient decided to undergo aggressive treatment with a triplet chemotherapy regimen of oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin (FOLFOXIRI) in combination with the anti–vascular endothelial growth factor receptor antibody bevacizumab.

The patient received 4 cycles of FOLFOXIRI plus bevacizumab. A follow-up CT scan showed a deep response to treatment. The metastatic disease in her liver had decreased by more than 50%, and her lymph nodes showed no evidence of disease. Her CEA level decreased to 9.5 U/mL. She underwent an additional 2 cycles of FOLFOXIRI plus bevacizumab, and her CEA level continued to decrease. She developed tolerable grade 2 peripheral neuropathy, as well as some myelosuppression, but was able to continue treatment without delay.

After completion of 6 cycles, the patient was switched to maintenance therapy with capecitabine plus bevacizumab. After 4 months, her disease progressed, as evidenced by enlarged lesions in the liver, as well as peritoneal nodules. The patient felt relatively well overall, although she reported some fatigue and abdominal discomfort. Her CEA level increased to 38 U/mL.

At this point, the patient and her oncologist discussed the next course of therapy. One possibility was the reintroduction of FOLFOXIRI, given that her progression-free interval was 4 months and she had few remaining options. However, she was experiencing some residual grade 1 neuropathy, and she was reluctant to receive further intravenous chemotherapy.

The patient and her oncologist decided to switch treatment to regorafenib. To avoid toxicity, an escalated dosing strategy was administered. The patient initiated regorafenib at a dose of 80 mg/day. She responded well to that dose, with no toxicities, and therefore was escalated to 120 mg/day. Over the following week, she developed grade 1 hand and foot syndrome reaction, as well as slightly more fatigue, but she was able to tolerate treatment. At the third week, the dose was escalated to 160 mg/day. She continued to do

On the Cover

Confocal light micrograph of cultured colorectal cancer cells dividing. The cellular proteins are indicated by fluorescent markers: DAPI (blue, cell nuclei), tubulin (green), and GM1 (red). The central island of flat cells (green) contains dividing cells and is surrounded by differentiated cells.

Credit: AMMRF, University of Sydney/Science Source.

Disclaimer

Table 1. Key Points of the Case

Initial Clinical Presentation
• A 53-year-old woman with an ascending colon mass with near complete obstruction
Pathology
• Microsatellite stable • *BRAF* V600E wild-type • *NRAS* wild-type • *HER2*-nonamplified • *KRAS* G13D mutation
Disease Characteristics
• Right-sided adenocarcinoma of the colon • Multiple liver metastases • Several positive retrograde peritoneal lymph nodes
Primary Treatment
• 6 cycles of FOLFOXIRI plus bevacizumab • Maintenance capecitabine plus bevacizumab
Second-Line Treatment
• Regorafenib

FOLFOXIRI, oxaliplatin, irinotecan, 5-fluorouracil, and leucovorin.

well at this dosage, with no further toxicities.

The patient continued treatment with regorafenib for 3 months. A follow-up CT scan showed that the existing lesions appeared stable, and no new lesions were evident. Her CEA level decreased back to 15 U/mL. She continued to receive regorafenib and had stable disease for another 8 months. At this point, a follow-up CT scan showed an increase in the size and number of her liver lesions, as well as newly involved lymph nodes. She proceeded to trifluridine/tipiracil next, with rapidly progressive disease. She then chose to proceed with hospice care.

Rationale for the Treatment Decisions

Chemotherapy combinations consisting of 5-fluorouracil (plus leucovorin) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) plus bevacizumab are widely considered the standard of care for the initial treatment of metastatic colorectal cancer (mCRC).[1] The efficacy and safety profiles of these combinations are largely similar, and thus the selection of their use in the first-line setting is usually based on physician and patient preference, regional differences, and the use of adjuvant oxaliplatin. Subsequently, phase 2 studies suggested that FOLFOXIRI was active and warranted further investigation.[2,3]

Establishing FOLFOXIRI in the First-Line Setting

Two phase 3 trials evaluated FOLFOXIRI in the first-line mCRC setting. These 2 studies, published within a year of each other, reported disparate results.

The Gastrointestinal Committee of the Hellenic Oncology Research Group compared FOLFOXIRI vs FOLFIRI as first-line treatment in patients with unresectable mCRC.[4] A total of 285 patients were randomly assigned to the 2 treatment arms. The primary endpoint was overall survival (OS). After a median follow-up of 26 months, the median OS was 21.5 months with FOLFOXIRI vs 19.5 months with FOLFIRI, a difference that did not reach statistical significance (*P*=.337). The median time to disease progression was 8.4 months with FOLFOXIRI vs 6.9 months with FOLFIRI (hazard ratio [HR], 0.83; 95% CI, 0.64-1.08; *P*=.17). The objective response rate (ORR) was 43% vs 33.6%, respectively (*P*=.168). The percentage of patients who proceeded to postchemotherapy radical (R0) surgery was 10% in the FOLFOXIRI arm vs 4% in the FOLFIRI arm (*P*=.08). There was no significant difference in grade 3/4 hematologic toxicities between the 2 arms. Grade 3/4 alopecia (*P*=.0001), diarrhea (*P*=.001), and neurosensory disorders (*P*=.001) were all more common with FOLFOXIRI compared with FOLFIRI.

The Gruppo Oncologico Nord Ovest also compared the FOLFOXIRI regimen with the FOLFIRI regimen in patients with previously untreated unresectable mCRC.[5] A total of 244 patients were randomly assigned to each treatment arm. At the initial analysis, the median follow-up was 18.4 months. ORR, the primary endpoint, was 60% with FOLFOXIRI vs 34% with FOLFIRI (*P*<.0001). The percentage of patients who were able to proceed to postchemotherapy radical (R0) surgery of metastases was 15% in the FOLFOXIRI arm vs 6% in the FOLFIRI arm (*P*=.033). The median progression-free survival (PFS) was 9.8 months with FOLFOXIRI vs 6.9 months with FOLFIRI (HR, 0.63; 95% CI, 0.47-0.81; *P*=.0006). The median OS was 22.6 months vs 16.7 months, respectively, with an HR for death of 0.70 (95% CI, 0.50-0.96; *P*=.032). Certain adverse events occurred at a significantly greater incidence with FOLFOXIRI vs FOLFIRI. Grade 3/4 neutropenia occurred in 50% vs 28% (*P*=.0006). In the final analysis of this study (at a median follow-up of 60.6 months), the benefits in OS and PFS observed with FOLFOXIRI vs FOLFIRI remained.[6] The median OS was 23.4 months vs 16.7 months (HR, 0.74; 95% CI, 0.56-0.96; *P*=.026), and the median PFS was 9.8 months vs 6.8 months (HR, 0.59; 95% CI, 0.45-0.76; *P*<.001).

The Addition of Bevacizumab to First-Line FOLFOXIRI

Given the benefit associated with adding bevacizumab to FOLFOX and FOLFIRI, the addition of bevacizumab to the FOLFOXIRI regimen was also assessed. This combination has been evaluated in several studies.

The phase 3 TRIBE trial, conducted in Italy, randomly assigned 508 patients with unresectable mCRC to receive either FOLFOXIRI or FOLFIRI, both administered with bevacizumab.[7] After 12 cycles of these

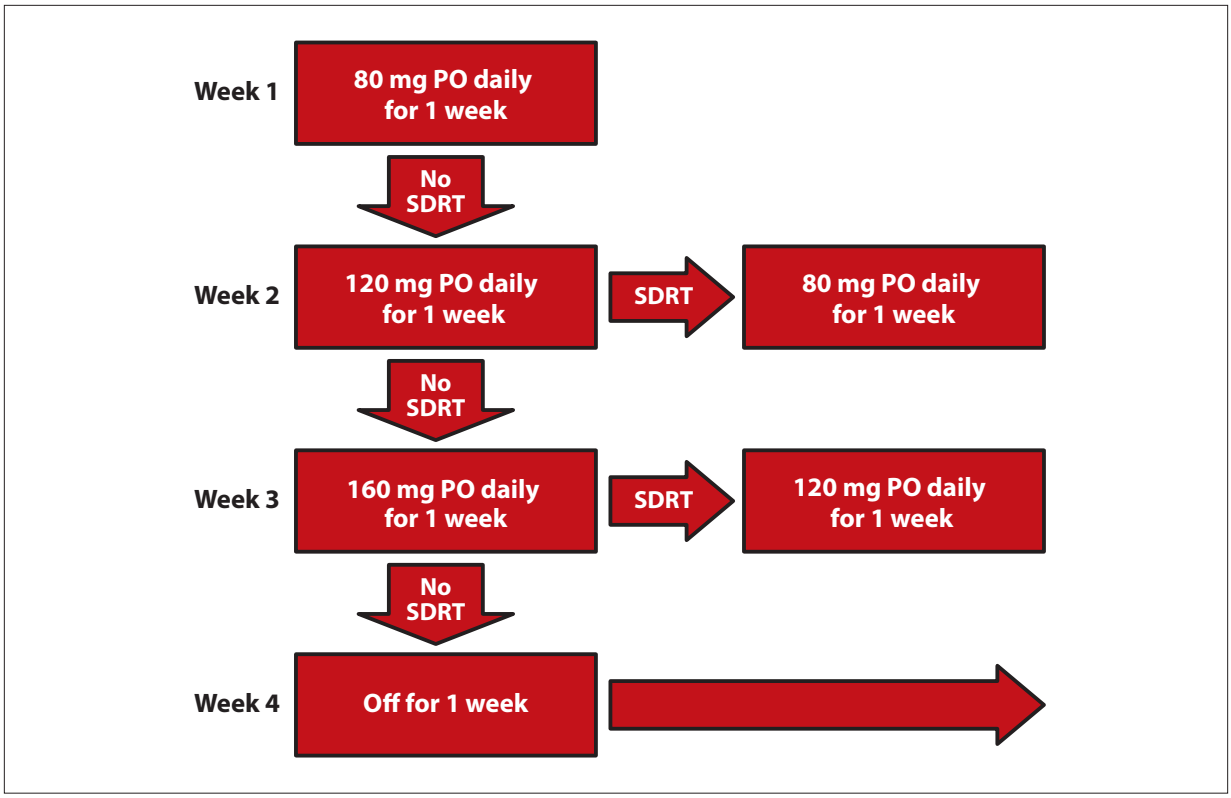

Figure 1. A dose-escalated strategy for the administration of regorafenib. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2015;13(8):514-517.[19]

regimens, maintenance treatment with 5-fluorouracil plus bevacizumab was administered until tumor progression. PFS was the primary endpoint. The median follow-up was 32.2 months. The median PFS was 12.1 months vs 9.7 months, respectively (HR, 0.75; 95% CI, 0.62-0.90; *P*=.003). The ORR was 65.1% vs 53.1% (odds ratio, 1.64; 95% CI, 1.15-2.35; *P*=.006). The proportion of patients who proceeded to R0 resection was 15% with FOLFOXIRI plus bevacizumab vs 12% with FOLFIRI plus bevacizumab (*P*=.33). The median OS was 31.0 months vs 25.8 months, a difference that was not statistically significant (HR, 0.79; 95% CI, 0.63-1.00; *P*=.054). In an updated survival analysis (median follow-up, 48.1 months), the benefit in the median OS did reach statistical significance, at 29.8 months with FOLFOXIRI plus bevacizumab vs 25.8 months with FOLFIRI plus bevacizumab (HR, 0.80; 95% CI, 0.65-0.98; *P*=0.03).[8] The incidences of grade 3/4 neutropenia, diarrhea, stomatitis, and peripheral neuropathy were higher with FOLFOXIRI plus bevacizumab.

The subsequent phase 3 TRIBE2 trial compared first-line FOLFOXIRI plus bevacizumab (followed by FOLFOXIRI plus bevacizumab in the second-line) vs the sequential use of mFOLFOX6 followed by FOLFIRI after disease progression (with both doublet regimens administered with bevacizumab).[9] The trial randomly assigned 679 patients to receive FOLFOXIRI plus bevacizumab or the sequential doublet. In both arms, maintenance treatment with 5-fluorouracil and leucovorin plus bevacizumab was administered until disease progression before second-line therapy was initiated. The median follow-up duration was 35.9 months. The primary endpoint of the study was PFS2, which referred to the time from randomization to disease progression on any treatment administered after first disease progression, or death from any cause. The median PFS2 was 19.2 months with FOLFOXIRI plus bevacizumab vs 16.4 months with the sequential doublets plus bevacizumab (HR, 0.74; 95% CI, 0.63-0.88; log-rank *P*=.0005). An objective response occurred in 62% vs 50%, respectively (odds ratio, 1.61; 95% CI, 1.19-2.18; *P*=.0023). R0 resection of metastases was possible in 17% vs 12% (odds ratio, 1.55; 95% CI, 1.00-2.39; *P*=.047). The median OS was 27.4 months with FOLFOXIRI plus bevacizumab vs 22.5 months with sequential doublets plus bevacizumab (HR, 0.82; 95% CI, 0.68-0.98; *P*=.032). During the first line of treatment, grade 3/4 adverse events were more frequent with FOLFOXIRI plus bevacizumab (68%) compared with the sequential doublets plus bevacizumab (46%).

A meta-analysis of the TRIBE and TRIBE2 trials, which also included individual patient data from the CHARTA, OLIVIA, STEAM trials, was recently

published.[10] These trials evaluated FOLFOXIRI in combination with bevacizumab for the first-line treatment of mCRC. The analysis included 846 patients treated with FOLFOXIRI plus bevacizumab and 851 treated with chemotherapy doublets plus bevacizumab. After a median follow-up of 39.9 months, the median OS was 28.9 months with FOLFOXIRI plus bevacizumab vs 24.5 months with chemotherapy doublets plus bevacizumab (HR, 0.81; 95% CI, 0.72-0.91; *P*<.001). First-line FOLFOXIRI plus bevacizumab also improved rates of PFS, overall response, and R0 resection rate. Grade 3/4 adverse events occurred with greater frequency with FOLFOXIRI plus bevacizumab.

Treatments After Progression During First-Line FOLFOXIRI Plus Bevacizumab

Despite the clear survival benefit demonstrated in both the TRIBE and TRIBE2 trials for the use of upfront FOLFOXIRI plus bevacizumab, concerns remain about the use of this regimen. The optimal treatment duration after disease progression during first-line FOLFOXIRI plus bevacizumab is not known, given that patients were exposed to both irinotecan and oxaliplatin. Several options may be appropriate in the second-line setting, including re-treatment with FOLFOXIRI plus bevacizumab (depending on the time interval to disease progression), doublet chemotherapy plus an antiangiogenic agent (bevacizumab, ramucirumab, or ziv-aflibercept), combinations incorporating an anti–epidermal growth factor receptor (EGFR) agent (cetuximab or panitumumab) for patients with wild-type *RAS*, or nonchemotherapy options typically reserved for later lines of treatment (regorafenib or trifluridine/tipiracil).

Guidelines from the National Comprehensive Cancer Network for patients treated with FOLFOXIRI in the first-line setting include irinotecan plus cetuximab or panitumumab (for *KRAS*/*NRAS*/*BRAF* wild-type tumors only), encorafenib plus cetuximab or panitumumab (for *BRAF* V600E mutation-positive tumors), regorafenib, or trifluridine/tipiracil administered with or without bevacizumab.[1] In addition, immunotherapy options are recommended for patients with tumors that are mismatch repair–deficient with high microsatellite instability. Anti–human epidermal growth factor receptor 2 (HER2) agents are recommended for patients with tumors that are HER2-amplified and *RAS* and *BRAF* wild-type.

A pooled analysis of the TRIBE and TRIBE2 studies focused on treatments for patients who developed progressive disease after first-line FOLFOXIRI plus bevacizumab.[11] Among 586 patients treated with this regimen, 524 developed disease progression after a median follow-up of 43.2 months. Of these, 419 patients (80%) received second-line treatment, which included FOLFOXIRI (with or without bevacizumab; 42%), a chemotherapy doublet (with or without bevacizumab; 29%), and an anti-EGFR-based regimen (57%). The median PFS2 was 6.1 months in those who received FOLFOXIRI with or without bevacizumab, 4.4 months in those treated with doublets with or without bevacizumab (HR, 0.76; 95% CI, 0.60-0.97; *P*=.029), and 3.9 months in those who received other treatments (HR, 0.71; 95% CI, 0.56-0.91; *P*=.007). The ORR was 23% with FOLFOXIRI with or without bevacizumab vs 11% with doublets with or without bevacizumab (odds ratio, 2.29; 95% CI, 1.18-4.42; *P*=.012). For other treatments, the ORR was 15%, a difference that did not reach statistical significance as compared with FOLFOXIRI (odds ratio, 1.67; 95% CI, 0.90-3.08; *P*=.10). The second OS did not differ between the second-line treatment groups (*P*=.558).

Regorafenib. The use of regorafenib in the third-line or later setting for mCRC has been well established in a number of prospective, randomized, controlled clinical trials.[12-15] Although these trials were conducted in a later-line setting, their findings may be applicable to patients treated with FOLFOXIRI in the first-line setting, as these patients have effectively been treated with chemotherapy agents traditionally administered as first- and second-line therapies.

The phase 3 CORRECT study was the pivotal trial that established the key registrational data for regorafenib.[12] The CORRECT study enrolled 760 patients from 16 countries (throughout North America, Europe, Asia, and Australia). The patients had mCRC with disease that progressed after treatment with all approved standard therapies. The number of prior therapies received for metastatic disease was 1 or 2 in 26%, 3 in 26%, and 4 or more in 48%. The patients were randomly assigned in a 2-to-1 ratio to receive regorafenib or placebo. The primary endpoint was overall survival. At the second planned interim analysis, the median OS was 6.4 months in the regorafenib arm vs 5.0 months in the placebo arm (HR, 0.77; 95% CI, 0.64-0.94; *P*=.0052). The secondary endpoint of median PFS was 1.9 months with regorafenib vs 1.7 months with placebo (HR, 0.49; 95% CI, 0.42-0.58; *P*<.0001). The ORR was low in both arms (1.0% with regorafenib vs 0.4% with placebo; *P*=.19), and all responses were partial. The disease control rate was 41% with regorafenib vs 15% with placebo (*P*<.0001).

The rate of treatment-related adverse events was 93% with regorafenib vs 61% with placebo. In the regorafenib arm, the most common adverse events of any grade were fatigue and hand-foot skin reaction. Grade 3/4 treatment-related adverse events occurred in 54% of the regorafenib arm vs 14% in the placebo arm. In the regorafenib arm, the most frequent of these events was hand-foot skin reaction (17%). Adverse events typically occurred during the first 2 cycles of treatment.

Among the 760 patients who were enrolled in the CORRECT trial, 111 (14.6%) were Asian (primarily Japanese).[12] The phase 3 CONCUR trial evaluated the clinical activity and safety of regorafenib in a broader population of Asian patients.[13] This study enrolled patients who developed progressive disease after receiving at least 2 prior lines of treatment, or who were intolerant to standard treatments. The patients were randomly assigned to treatment with regorafenib or placebo. The primary endpoint was OS. Despite the different patient population, the results of the CONCUR trial mirrored those of CORRECT. The median OS was 8.8 months with regorafenib vs 6.3 months with placebo (HR, 0.55; 95% CI, 0.40-0.77; one-sided *P*=.00016). The median PFS was 3.2 months vs 1.7 months, respectively (HR, 0.31; 95% CI, 0.22-0.44; *P*<.0001). No responses were observed with placebo. In the regorafenib arm, the ORR was 4%; all responses were partial. The disease control rate was 51% in the regorafenib arm vs 7% in the placebo arm (one-sided *P*<.0001). Treatment-related adverse events occurred in 97% of the regorafenib arm vs 46% of the placebo arm. Grade 3 or higher treatment-related adverse events occurred in 54% vs 15%, respectively. The most frequent of these events in the regorafenib arm was hand-foot skin reaction (16%).

The CONSIGN study further characterized the safety profile of regorafenib.[14] This prospective, single-arm, observational study enrolled 2864 patients with treatment-refractory mCRC and an ECOG performance status of 0 or 1. The primary endpoint was safety. Overall, 87% of patients required some type of dose modification; a mean of 20% of the planned dose was administered. Treatment-emergent adverse events led to dose reductions in 46% of patients and to treatment discontinuation in 9%. The most common grade 3 or higher treatment-related adverse events were hypertension (15%), hand-foot skin reaction (14%), and fatigue (13%). The median PFS was 2.7 months (95% CI, 2.6-2.7).

The phase 2 randomized ReDOS trial evaluated the safety and activity of an alternative regorafenib dosing schedule.[15] The trial enrolled 123 patients with refractory mCRC and an ECOG performance status of 0 or 1. The patients were randomly assigned to 4 arms: regorafenib administered at the standard dose, regorafenib administered in an escalated-dosing strategy, clobetasol applied preemptively, and clobetasol applied reactively. Because clobetasol lacked a significant treatment effect, the data were pooled to compare the 2 dosing strategies for regorafenib. The standard regorafenib dose strategy was 160 mg/day for 21 days of a 28-day cycle. The dose-escalation strategy began at 80 mg per day (Figure 1). The dose was escalated weekly in 40-mg increments up to 160 mg/day in the absence of treatment-related adverse events. The primary endpoint was the proportion of evaluable patients (defined as those who were eligible, consented, and received any protocol treatment) initiating cycle 3 and was analyzed per protocol.

The primary endpoint was met by 43% of patients in the dose-escalation arm vs 26% of patients in the standard-dose arm (one-sided *P*=.043). The primary reason for not initiating a third cycle of treatment was disease progression (reported in 37% of the dose-escalation arm vs 47% of the standard-dose arm), followed by adverse events (11% vs 8%). Grade 3 toxicities typically associated with regorafenib, including fatigue, hand-foot skin reaction, hypertension, and diarrhea, were generally lower with the dose-escalation strategy vs the standard-dosing strategy across the first 2 cycles of therapy. After a median follow-up of 1.18 years, the median OS was 9.8 months in the dose-escalation arm vs 6.0 months in the standard-dose arm (HR, 0.72; 95% CI, 0.47-1.10; log-rank *P*=.12). The median PFS was similar between the 2 arms (2.8 vs 2.0 months; HR, 0.84; 95% CI, 0.57-1.24; log-rank *P*=.38). Overall, the study investigators concluded that the dose-escalation strategy of regorafenib was active and could potentially reduce the incidence of several of the higher-grade adverse events typically associated with regorafenib.

The prospective phase 2 PREVIUM trial investigated the use of regorafenib as second-line treatment following the first-line use of FOLFOXIRI plus bevacizumab.[16] The study enrolled patients with mutated *KRAS* or *BRAF* tumors. The primary endpoint was PFS, and the secondary endpoint was OS. Although the trial was closed prematurely based on poor patient accrual (15 patients enrolled), initial observations have been published. The median PFS was 2.2 months, the median time to disease progression was 2.0 months, and the median OS was 3.3 months. No patient remained progression-free at 6 months. Dose reduction was required in 7 patients (47%), primarily for asthenia (43%). The most common regorafenib-related grade 3 adverse events were asthenia (33%), dysphonia (13%), and hypertension (13%). No grade 4 adverse events were reported.

According to the PREVIUM investigators, the lower clinical activity (compared with the pivotal CORRECT study) may be attributed to the clinical and molecular high-risk and poor-prognosis features of the study population.[16] For example, the median time to disease progression during treatment with first-line FOLFOXIRI plus bevacizumab was short (<14 months), and circulating tumor cell counts higher than 3 per 7.5 mL were reported in 87% of patients. The study investigators suggested that future clinical trials exploring regorafenib in the second-line setting should refine the patient population.

Trifluridine/tipiracil. The drug combination trifluridine/tipiracil (also known as TAS-102) may be used after first-line

treatment with FOLFOXIRI plus bevacizumab.[17] This regimen was evaluated in the pivotal RECOURSE trial, which randomly assigned 800 patients to trifluridine/tipiracil or placebo. All patients had refractory mCRC after at least 2 lines of therapy. The median OS, the primary endpoint of the study, was 7.1 months with trifluridine/tipiracil vs 5.3 months with placebo (HR, 0.68; 95% CI, 0.58-0.81; *P*<.001). The median PFS was 2.0 months vs 1.7 months, respectively (HR, 0.48; 95% CI, 0.41-0.57; *P*<.001). The ORR was 1.6% vs 0.4% (*P*=.29). Grade 3 or higher toxicities occurred in 69% of the trifluridine/tipiracil arm vs 52% of the placebo arm. In the trifluridine/tipiracil arm, these events included neutropenia (38%), anemia (18%), and thrombocytopenia (5%), all of which were higher than in the placebo arm. The incidence of grade 3 or higher gastrointestinal toxicities was also higher with trifluridine/tipiracil.

Data for the addition of bevacizumab to trifluridine/tipiracil was recently reported in a phase 2 trial by Pfeiffer and colleagues.[18] The trial enrolled patients with mCRC in Denmark. The patients were randomly assigned to receive trifluridine/tipiracil alone or in combination with bevacizumab. The primary endpoint was PFS. The median PFS was 2.6 months in patients treated with trifluridine/tipiracil alone vs 4.6 months in patients treated with trifluridine/tipiracil plus bevacizumab (HR, 0.45; 95% CI, 0.29-0.72; *P*=.0010). The median OS was 6.7 months vs 9.4 months, respectively (HR, 0.55; 95% CI, 0.32-0.94; *P*=.028). The addition of bevacizumab increased the rate of grade 3 or higher neutropenia from 38% in the monotherapy arm to 67% in the combination arm.

Disclosure

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