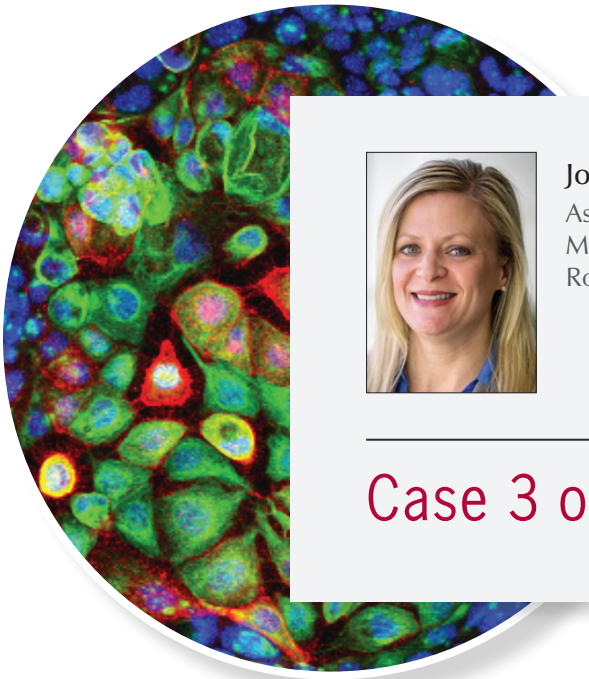
Case Study Series

Clinical Advances in Hematology & Oncology April 2021

Cases in the Management of Metastatic Colorectal Cancer: Rechallenge With Chemotherapy After Regorafenib in a Patient With *RAS/BRAF* Wild-Type Disease



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Case 3 of a 3-Part Series

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Cases in the Management of Metastatic Colorectal Cancer: Rechallenge With Chemotherapy After Regorafenib in a Patient With *RAS*/*BRAF* Wild-Type Disease

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Patient Case

The patient is a 50-year-old man who had been diagnosed with left-sided colon cancer 4 years earlier (Table 1). At the time of his diagnosis in January 2016, positron emission tomography (PET)/computed tomography (CT) identified 2 hepatic lesions. The patient initiated perioperative chemotherapy with 6 cycles of folinic acid, fluorouracil, and oxaliplatin (FOLFOX). After completing 6 chemotherapy cycles, the patient achieved an excellent response and proceeded to undergo a left hepatectomy. After an additional 6 cycles of FOLFOX, he underwent a left hemicolectomy. Pathologic examination of this surgical resection revealed a pT3N2b lesion that had penetrated through the muscularis propria layer and into the subserosa. Pathologic examination also confirmed that 12 of 27 lymph nodes were positive for micrometastatic disease.

Follow-up PET/CT in March 2017 revealed a new lesion in the liver. The patient started first-line chemotherapy with 8 cycles of folinic acid, fluorouracil, and irinotecan (FOLFIRI), and then proceeded to surgical resection of the liver lesion. After this treatment, he was followed with observation.

In March 2019, the patient was noted to have a new liver lesion, several positive nodules in the chest, and a soft-tissue nodule in the pelvis that was next to, but separate from, the rectum. A specimen was obtained from the pelvic nodule and submitted for next-generation sequencing, which revealed that his tumor was all *RAS* wild-type, *BRAF* wild-type, human epidermal growth factor receptor 2 (HER2)-negative, and microsatellite-stable.

Given that his tumor was on the left side of the colon and *RAS/BRAF* wild-type, in May 2019, the patient started treatment with FOLFIRI plus panitumumab. He did well on this regimen, and achieved a partial response. In December 2019, treatment was changed to single-agent panitumumab. The patient continued maintenance therapy for several months, until July 2020, when he developed a new lesion in the liver.

We presented the patient with a few options for third-line treatment. We recommended initiation of regorafenib, with the hope that this agent could potentially re-sensitize the tumor to subsequent anti–epidermal growth factor receptor (EGFR) therapy. This recommendation was also based on the observation that regorafenib could be more effective when it is used in the true third-line setting.

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.

Table 1. Key Points of the Case

Initial Clinical Presentation
• A 50-year-old man who had been diagnosed with left-sided colon cancer 4 years earlier
Pathology
• Among 27 lymph nodes, 12 were positive for micrometastatic disease • All RAS wild-type (without mutations in *KRAS*, *HRAS*, or *NRAS*) • *BRAF* wild-type • HER2-negative • Microsatellite-stable
Disease Characteristics
• A pT3N2b lesion that had penetrated through the muscularis propria layer and into the subserosa
Primary Treatments
• Perioperative chemotherapy with FOLFOX • Left hepatectomy • Left hemicolectomy • FOLFIRI • Surgical resection of a liver lesion
Lines of Therapy for Metastatic Disease
• FOLFIRI plus panitumumab • Panitumumab • Regorafenib • Irinotecan plus panitumumab

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

The patient began treatment with regorafenib in July 2020. We followed the dose-escalation strategy, starting treatment at 80 mg daily, then raising the dose first to 120 mg and then to 160 mg. The patient tolerated the 160 mg daily dose for approximately 2 months, but the dose was reduced back to 120 mg owing to an increase in diarrhea. He achieved stable disease with few adverse events. The disease remained stable for several months.

In October 2020, a PET/CT scan revealed a new liver lesion. The patient then began fourth-line treatment with irinotecan plus panitumumab. A repeat scan in January 2021 showed that his overall tumor burden had decreased by more than 50%. One of the liver lesions that had measured 5.2 × 3.7 cm decreased to 1.9 × 2.0 cm. The soft-tissue pelvic nodule that was originally 2.6 × 2.9 cm decreased to 1.8 × 2.3 cm. The patient achieved a marked response of more than 50% to this fourth-line regimen, which is higher than that expected with just the chemotherapy alone. Although it cannot be stated for certain that regorafenib re-sensitized the tumor to chemotherapy, this possibility is consistent with other reports in the literature regarding the use of an EGFR inhibitor after regorafenib.[1]

This case study highlights the potential for the appropriate use of regorafenib in the third-line setting. It also suggests that regorafenib may play a role in re-sensitizing a tumor to chemotherapy plus an EGFR inhibitor and justifies a rechallenge of these agents.

Rationale for the Treatment Decisions

The patient began treatment for colorectal cancer (CRC) with FOLFOX and surgery. A year after his initial diagnosis, a new lesion was found in his liver. The patient then received FOLFIRI as first-line treatment for metastatic disease. For many years, FOLFIRI has been known to be an effective and well-tolerated treatment in this setting.[2] The patient underwent surgical resection of the liver lesion, followed by observation.

Approximately 2 years later, the patient was diagnosed with a new liver lesion, positive nodules in the chest, and a soft-tissue nodule in the pelvis that was next to the rectum. Next-generation sequencing showed that the tumor was all *RAS* wild-type, *BRAF* wild-type, HER2-negative, and microsatellite-stable.

The patient then began treatment with FOLFIRI plus panitumumab. In a global, open-label, randomized phase 3 trial, the addition of panitumumab to FOLFIRI improved outcome vs FOLFIRI alone in patients with *KRAS* wild-type metastatic CRC.[3] The trial enrolled all comers, and *KRAS* status was available for 91% of patients. *KRAS* wild-type disease was reported in 597 patients. Among these patients, the median progression-free survival was 5.9 months with FOLFIRI plus panitumumab vs 3.9 months with FOLFIRI alone (hazard ratio [HR], 0.73; 95% CI, 0.59-0.90; *P*=.004). The median overall survival was 14.5 months with panitumumab plus FOLFIRI vs 12.5 months with FOLFIRI alone, but this difference did not reach statistical significance (HR, 0.85; 95% CI, 0.70-1.04; *P*=.12). The objective response rate was 35% in the panitumumab-plus-FOLFIRI arm vs 10% in the FOLFIRI arm (descriptive *P*<.001). A difference in efficacy did not emerge for patients with the *KRAS* mutation.

Approximately 7 months later, FOLFIRI was stopped, and the patient continued treatment with panitumumab. In an open-label phase 3 trial, the addition of panitumumab to best supportive care improved outcome in patients with chemotherapy-refractory metastatic CRC.[4] The median progression-free survival was 8 weeks (95% CI, 7.9-8.4) with panitumumab plus best supportive care vs 7.3 weeks (95% CI, 7.1-7.7) with best supportive care alone. The mean duration of progression-free survival was

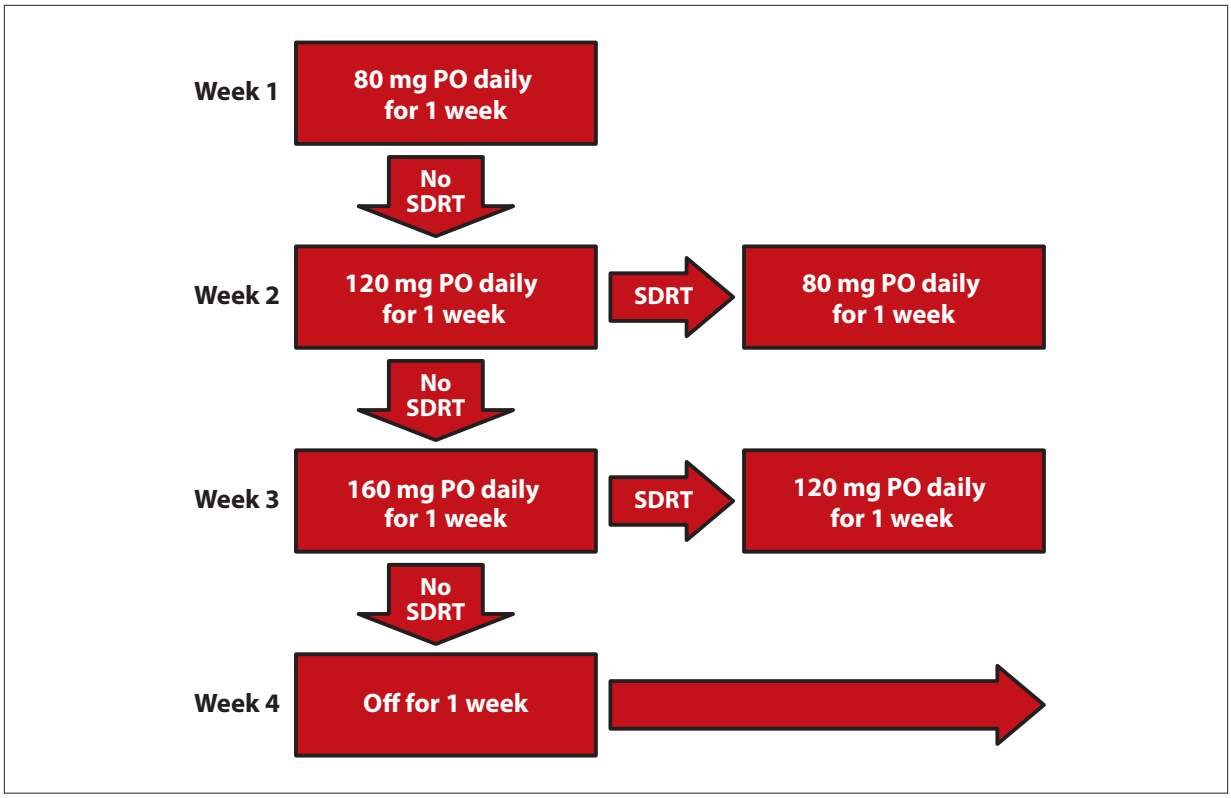

Figure 1. A dose-escalated strategy for the administration of regorafenib. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2015;13(8):514-517.[16]

13.8 weeks (standard error, 0.8) vs 8.5 weeks (standard error, 0.5), respectively. After follow-up of 12 months or longer, the objective response rate was 10% vs 0% (*P*<.0001). There was no difference in overall survival (HR, 1.00; 95% CI, 0.82-1.22), but the investigators noted that the analysis of this endpoint was confounded by similar activity of panitumumab after 76% of patients in the best supportive care arm crossed over to receive panitumumab.

A retrospective biomarker analysis of this study showed a clear benefit for patients with *KRAS* wild-type tumors.[5] Among these patients, progression-free survival was 12.3 weeks with panitumumab plus best supportive care vs 7.3 weeks for best supportive care alone (HR, 0.45; 95% CI, 0.34-0.59; *P*<.0001). In patients with mutated tumors, progression-free survival was 7.4 weeks vs 7.3 weeks (HR, 0.99; 95% CI, 0.73-1.36).

Among patients with *KRAS* wild-type disease, panitumumab was shown to be noninferior to cetuximab in a phase 3 trial.[6] Overall survival was 10.4 months with panitumumab vs 10 months with cetuximab (HR, 0.97; 95% CI, 0.84-1.11; *P*=.0007).

Several months later, the patient developed a new lesion in the liver. Third-line treatment with regorafenib was initiated.

Use of Regorafenib in the True Third-Line Setting

The oral multikinase inhibitor regorafenib blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis, oncogenesis, and the tumor microenvironment.[7] In the United States, regorafenib is approved by the US Food and Drug Administration for the treatment of metastatic CRC in patients 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-EGFR therapy.[8] Since the efficacy and safety of regorafenib were established in the CORRECT and CONCUR studies,[9,10] multiple other studies have further explored the use of this agent for metastatic CRC.

In this patient, regorafenib was administered following the dose-escalation strategy from the ReDOS trial (Figure 1).[11] Guidelines from the National Comprehensive Cancer Network endorse this strategy for the use of regorafenib.[12] The randomized phase 2 ReDOS study established that a dose-escalating strategy for regorafenib provided similar efficacy with improved safety outcomes.[11] In the ReDOS trial, regorafenib was initiated at a dose of 80 mg once daily on days 1 to 7. Among patients without drug-related toxicities, the dose was then escalated to 120 mg once daily on days 8 to 14, followed by 160 mg once

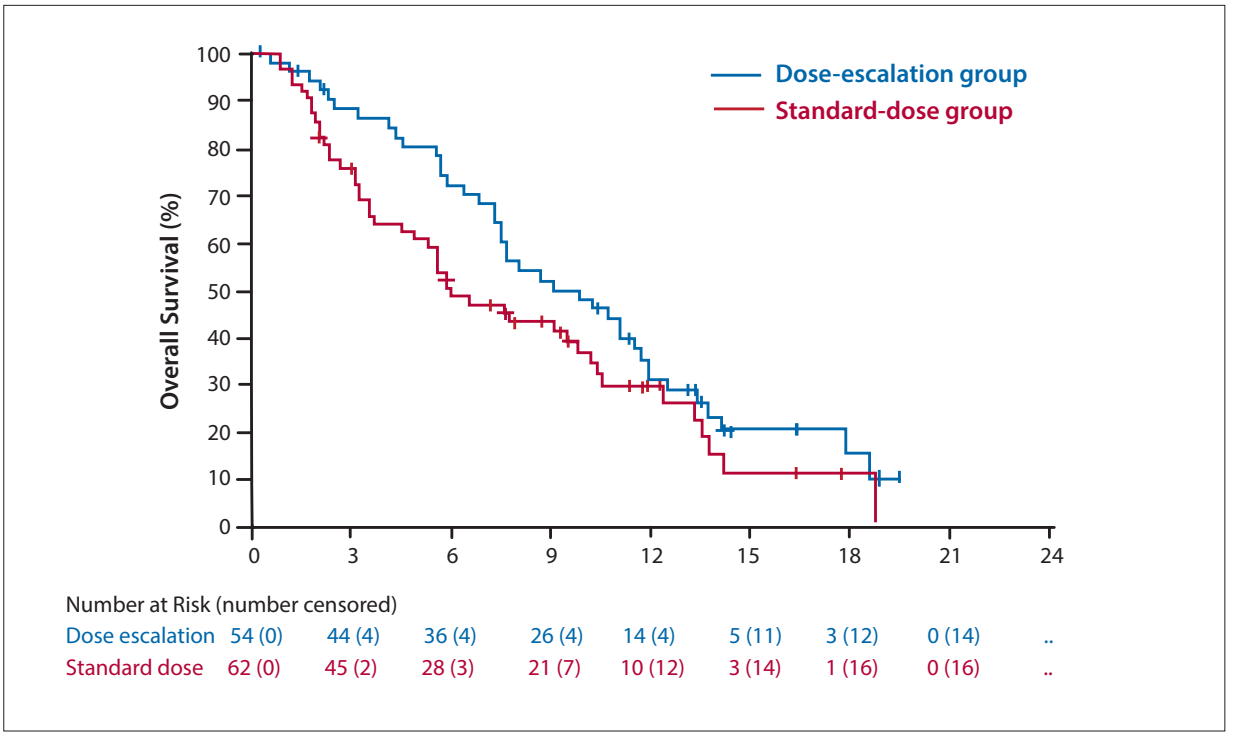

Figure 2. Overall survival in the randomized phase 2 ReDOS trial, which evaluated a dose-escalated regimen of regorafenib. In the dose-escalated arm, regorafenib was initiated at 80 mg/day. The dose was increased weekly up to 160 mg/day in patients without significant drug-related toxicities. In the standard-dose arm, the dose of regorafenib was 160 mg/day. Adapted from Bekaii-Saab TS et al. *Lancet Oncol*. 2019;20(8):1070-1082.[11]

daily on days 15 to 21. In subsequent cycles, treatment consisted of the highest tolerated dose from cycle 1. The investigators compared this alternative-dosing strategy against the standard-dosing strategy. The primary endpoint was the proportion of evaluable patients initiating cycle 3. Among 116 evaluable patients, this endpoint was met by 43% of those in the dose-escalated arm vs 26% of those in the standard-dosing arm (P=.043). The median overall survival was 9.8 months vs 6.0 months, a difference that did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank P=.12; Figure 2). No difference was observed in progression-free survival (HR, 0.84; 95% CI, 0.57-1.24; log-rank P=.38).

During the first 2 cycles of treatment, patients in the dose-escalated arm experienced lower rates of grade 3 adverse events, including fatigue, hand-foot skin reaction, hypertension, and diarrhea. Among grade 3/4 adverse events, the most common 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%). Quality-of-life scores were similar between the 2 dosing arms at baseline. By the second week of treatment, patients in the dose-escalation arm had significantly better mean quality-of-life scores (as assessed with the Brief Fatigue Inventory questionnaire). Improvements were seen in measures such as current fatigue, general activity interference, mood interference, walking ability interference, and normal work interference. At weeks 4, 6, and 8, however, there were no significant differences in quality-of-life scores.

REVERCE was a randomized phase 2 study that compared the sequence of regorafenib followed by cetuximab vs the reverse sequence (cetuximab followed by regorafenib) in the third-line setting in patients with previously treated metastatic CRC.[13] The trial enrolled patients with an Eastern Cooperative Oncology Group performance status of 0 to 2, and measurable or non-measurable disease (per Response Evaluation Criteria in Solid Tumors v1.1). Additionally, patients were *KRAS* wild-type (exon 2 codon 12 or 13). Patients had received previous treatment with fluoropyrimidines, oxaliplatin, and irinotecan, which resulted in inadequate responses. Patients were naive to anti-EGFR antibodies.

A total of 101 patients were randomly assigned in a 1-to-1 ratio to treatment with either regorafenib followed by cetuximab or the reverse sequence of cetuximab followed by regorafenib.[13] In both cases, patients were switched to their second treatment upon disease progression. Interestingly, the median overall survival was longer for patients treated with regorafenib first compared with

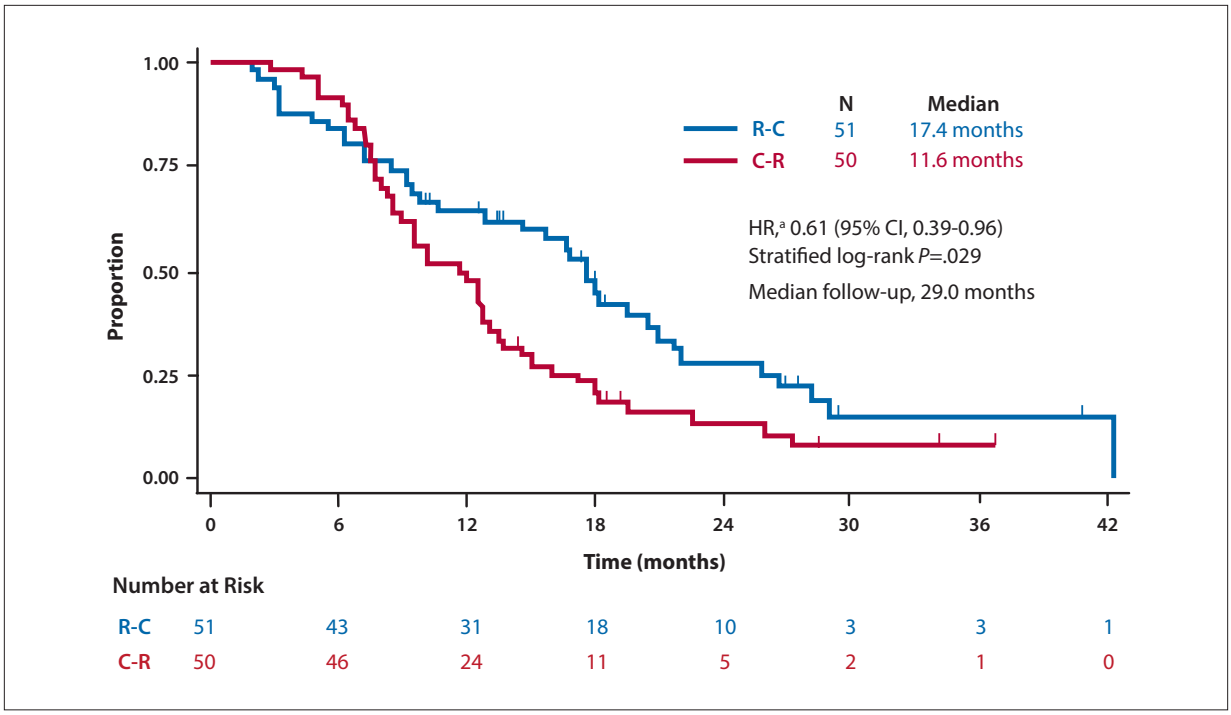

Figure 3. Overall survival in the phase 2 study REVERCE trial, which compared the sequence of regorafenib followed by cetuximab (R-C) vs the sequence of cetuximab followed by regorafenib (C-R). [a]Adjusted by intention to use irinotecan. HR, hazard ratio. Adapted from Shitara K et al. *Ann Oncol.* 2019;30(2):259-265.[13]

patients treated with cetuximab first, at 17.4 months vs 11.6 months, respectively (HR, 0.61; 95% CI, 0.39-0.96; stratified log-rank *P*=.0293; Figure 3). Other endpoints were also longer in the rituximab-first arm, including the median time to failure of the sequential treatment (7.4 months vs 6.1 months; HR, 0.60; 95% CI, 0.39-0.92; *P*=.017). The median progression-free survival for the entire sequential treatment was 9.0 months in the regorafenib-first arm, compared with 7.1 months in the cetuximab-first arm (HR, 0.55; 95% CI, 0.34-0.90; *P*=.015). In the regorafenib-first arm, grade 3 or higher nonhematologic toxicities occurred in 71% of patients during regorafenib treatment and in 50% of patients during cetuximab treatment. In the cetuximab-first arm, the rates of grade 3 or higher nonhematologic toxicities were 57% during cetuximab treatment and 63% during regorafenib treatment.

The improved overall survival reported in the REVERCE trial when regorafenib was administered in the true third-line setting was intriguing. These results have led to speculation that regorafenib could potentially impact the tumor biology in such a way as to make it more sensitive to subsequent EGFR inhibition.

Adding further data to this hypothesis are results from the IMblaze370 study.[14] IMblaze370 was an overall negative study, but there are several important points to glean from the data. The study was designed with a 3-arm randomization, in which patients were randomly assigned in a 2-to-1-to-1 ratio to third-line treatment with either the anti–programmed death ligand 1 immunotherapy agent atezolizumab plus the MEK inhibitor cobimetinib, atezolizumab monotherapy, or regorafenib (considered the standard of care in this study). The median overall survival was 8.51 months with regorafenib, 7.10 months with atezolizumab monotherapy, and 8.87 months with atezolizumab plus cobimetinib. The hazard ratios were 1.00 (95% CI, 0.73-1.38; *P*=.99) for atezolizumab plus cobimetinib vs regorafenib and 1.19 (95% CI, 0.83-1.71; *P*=.34) for atezolizumab vs regorafenib. The median overall survival with third-line regorafenib in IMblaze370 was longer than that previously reported in the pivotal phase 3 CORRECT study (6.4 months).[9] In the CORRECT trial, however, regorafenib was used in the third-line or later setting; 25% of patients randomly assigned to regorafenib had received 3 prior systemic anticancer therapies for metastatic disease, and 49% of the regorafenib arm had received 4 or more prior treatments.

Preclinical data have demonstrated that treatment with an anti-EGFR agent causes the death of cancer cells that have a *RAS* wild-type background, with an accompanying increase in new cells with a mutated *RAS* gene that are more resistant to EGFR blockade.[15] Accordingly, a

treatment break from the anti-EGFR therapy corresponds to a decrease in these resistance mechanisms over time, with the potential to re-sensitize the tumor to treatment with an EGFR inhibitor.[1]

Disclosure

Dr Hubbard has performed contracted research with the following companies, with all payments going directly to Mayo Clinic: Boston Biomedical, Effector, Senhwa Biosciences, Merck, Treos Bio, Bayer, Hutchison MediPharma, TriOncology, Trovagene, Incyte, and Taiho.

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