

CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

Section Editor: Axel Grothey, MD

Emerging Phase 3 Data in Relapsed/Refractory Metastatic Colorectal Cancer



Richard Goldberg, MD
 Interim Division Director of Medical Oncology
 Physician-in-Chief, OSUCCC-James Cancer Hospital and Solove Research Institute
 Klotz Family Chair of Cancer Research
 Professor, Internal Medicine, College of Medicine
 The Ohio State University
 Wexner Medical Center
 Columbus, Ohio

H&O How many patients with metastatic colorectal cancer develop relapsed/refractory disease?

RG Most patients with metastatic colorectal cancer are not curable. A subset of patients have oligometastatic disease, which is characterized by a few lesions usually confined to a single organ (most commonly the liver) that can be resected for cure. (Exactly how many lesions constitute resectable disease is an individualized decision based on the patient's anatomy, disease burden, and the consensus of the multidisciplinary management team.) In the N9741 trial and other large series evaluating combination chemotherapy with or without biologic agents in metastatic patients, approximately 10% of patients were alive at 5 years. Some of these patients will be long-term survivors. However, 90% of patients with metastatic colorectal cancer will eventually develop relapsed or refractory disease. Therefore, a very large number of patients in clinical practice require alternatives to treatment after they exhaust standard chemotherapy.

H&O What types of treatments are available for these patients?

RG In general, patients with relapsed/refractory metastatic colorectal cancer are treated with multiple lines of chemotherapy. Patients who do not have a *RAS* mutation can be treated with monoclonal antibodies targeting the epidermal growth factor receptor (EGFR), such as panitumumab (Vectibix, Amgen) or cetuximab (Erbix, Lilly). These

agents are not effective in patients with *RAS* mutations, who therefore have fewer options.

Two oral agents have been shown to extend survival in refractory patients with or without a *RAS* mutation. The targeted agent regorafenib (Stivarga, Bayer HealthCare) is a tyrosine kinase inhibitor that hits multiple pathways. It also inhibits serine-threonine kinases (such as BRAF). Regorafenib was approved by the US Food and Drug Administration (FDA) in 2012 for patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-vascular endothelial growth factor (VEGF) therapy; and an anti-EGFR therapy (if the patient is *KRAS* wild-type). In 2015, the FDA approved a combination agent consisting of trifluridine and tipiracil (Lonsurf, Taiho Oncology), formerly known as TAS-102, for a similar patient population. It is a cytotoxic therapy. Both regorafenib and TAS-102 offer patients possibilities for late-line treatment.

A less common option for relapsed/refractory patients is a locally directed procedure. Patients with liver-dominant disease sometimes receive an injection of radioactive yttrium-90 into the liver in an attempt to control disease. Yttrium-90 has no effect on extrahepatic disease.

H&O How does regorafenib differ from traditional cytotoxic chemotherapy?

RG Cytotoxic chemotherapy targets DNA division and tries to force cells to undergo apoptosis during division.

Targeted therapies, such as regorafenib, aim to turn off the switch that drives the cells to divide. Regorafenib has a broad mechanism of action. It hits several tyrosine kinases that are relevant to colon cancer replication, such as VEGF receptors 1 through 3, TIE2, platelet-derived growth factor receptor β , fibroblast growth factor receptors, *KIT*, and *RET*. Regorafenib can therefore target tumor cells with multiple mutations. One issue in patients with refractory disease is that a tumor exposed to chemotherapy and targeted agents may, in response to evolutionary pressure, evolve into multiple cell lines that can be refractory to a single treatment. With its broad mechanism of action, regorafenib can potentially suppress resistant clones not susceptible to a single drug with a single target.

H&O What data support the use of the newer agents?

RG The phase 3 RECURSE (Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) trial evaluated TAS-102 in patients with metastatic colorectal cancer. Patients were refractory to antitumor therapy or had experienced clinically significant adverse events that precluded the readministration of antitumor therapies. The study randomly assigned 534 patients to receive TAS-102 and 266 to receive placebo. The median overall survival was 7.1 months with TAS-102 vs 5.3 months with placebo (hazard ratio [HR], 0.68; 95% CI, 0.58-0.81; $P < .001$). The 1-year overall survival rates were 27% for the TAS-102 group and 18% for the placebo group. Median progression-free survival in the TAS-102 arm was 2.0 months vs 1.7 months in the placebo arm (HR, 0.48; 95% CI, 0.41-0.57).

Several trials have provided data on regorafenib. The CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial, which led to the FDA approval of regorafenib, showed advantages in progression-free survival and overall survival in patients with refractory disease. Median overall survival was 6.4 months with regorafenib vs 5.0 months with placebo (HR, 0.77; 95% CI, 0.64-0.94; 1-sided $P = .0052$). Median progression-free survival was 2.0 months with regorafenib vs 1.7 months with placebo.

The CONCUR (Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial followed a design similar to that of CORRECT. It was conducted in Asian countries, excluding Japan. (The CORRECT trial enrolled patients of Japanese ancestry, but not patients from other Asian countries.) In addition, the population in CONCUR was less heavily pretreated. The results of CONCUR were similar to those of CORRECT. Regorafenib was associated with few partial remissions, but it improved progression-free

survival and overall survival, suggesting that Asian patients benefit in the same way as patients from the rest of the world. Median overall survival was 8.8 months in the regorafenib arm vs 6.3 months in the placebo arm (HR, 0.55; 95% CI, 0.40-0.77; 1-sided $P = .00016$; see the figure). Median progression-free survival was 3.2 months vs 1.7 months, respectively (HR, 0.311; 95% CI, 0.222-0.435; 1-sided $P < .0001$).

A registry study, known as CONSIGN (Regorafenib in Subjects With Metastatic Colorectal Cancer [CRC] Who Have Progressed After Standard Therapy), was designed to collect additional information about the toxicity and activity of regorafenib in the real-world setting of clinical practice. CONSIGN enrolled 2872 patients, from 188 sites in 25 countries, who had progressed after standard therapies for metastatic colorectal cancer. The registry confirmed data from randomized trials showing that regorafenib has a consistent activity and toxicity profile. The estimated progression-free survival with regorafenib was 2.8 months.

H&O What are the toxicity profiles of these agents?

RG In the phase 3 trial of TAS-102, grade 3 or higher adverse events occurred in 69% of the treatment arm vs 52% of the placebo arm. Among the patients who received TAS-102, 38% developed neutropenia of grade 3 or higher, 4% had febrile neutropenia, and 9% received granulocyte colony-stimulating factor. There was 1 treatment-related death (from septic shock). Grade 3 or higher anemia occurred in 18% of the TAS-102 arm vs 3% of the placebo arm. Grade 3 or higher thrombocytopenia was also more frequent in the TAS-102 group (5% vs $< 1\%$).

In the phase 3 CORRECT trial, treatment-related adverse events occurred in 93% of patients assigned to regorafenib vs 61% of those assigned to placebo. The most common grade 3 or higher adverse events related to regorafenib were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or desquamation (6%).

H&O What is the approved dosing for regorafenib, and how has it evolved in clinical practice?

RG Clinical experience with regorafenib has raised questions regarding tolerance at the dosage listed on the package insert, which is 160 mg/day for 3 weeks out of 4. This dosage has proven to be a challenge for many patients, primarily owing to fatigue, hand-foot syndrome, poor appetite, and hoarse voice. Like many physicians who prescribe regorafenib, I often start patients at a lower dose, such as 80 mg/day. If the lower dose is tolerated, I then consider escalating the dosage to up to 160 mg/day.

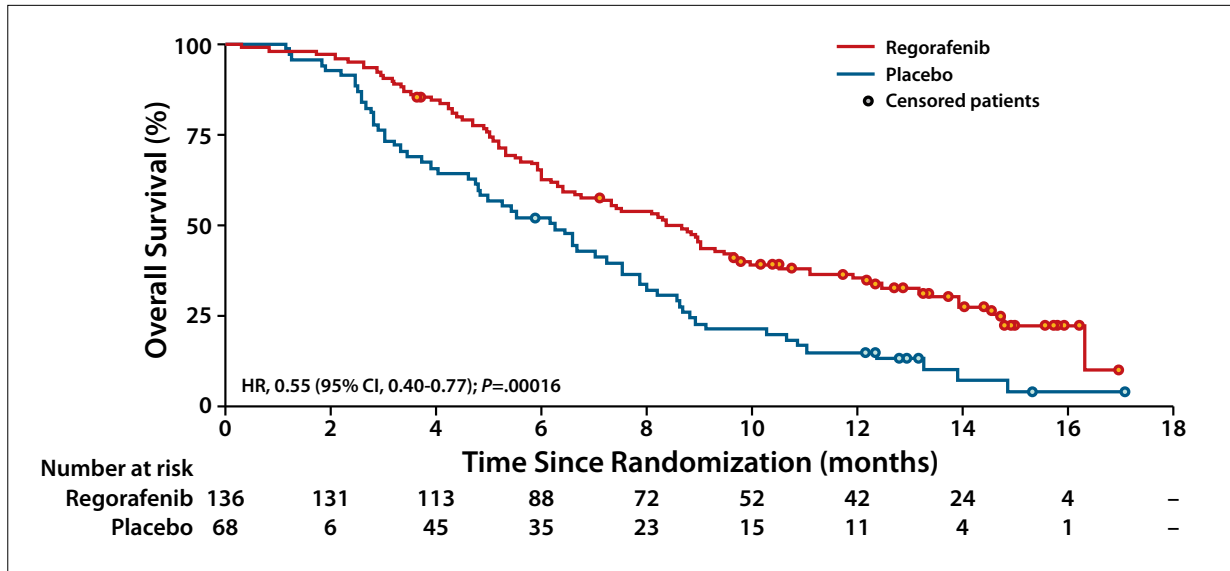


Figure. Overall survival in the CONCUR trial, which compared regorafenib vs placebo in Asian patients with progressive metastatic colorectal cancer. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Li J et al. *Lancet Oncol.* 2015;16(6):619-629.

The ReDOS (Regorafenib Dose Optimization Study) study is currently evaluating a lower dose of regorafenib in patients with refractory metastatic colorectal cancer. A standard arm employing 160 mg/day is being compared with an experimental arm, which has a starting dose of 80 mg/day with weekly escalations of 40 mg/day according to tolerability until 160 mg/day or the maximum tolerated dose is reached.

H&O Are there any characteristics that might suggest a patient will benefit from regorafenib?

RG Regorafenib improves outcome in only a subset of patients, and it would be helpful to restrict its use to those patients most likely to benefit. There are several clinical indicators of patients who are more likely to benefit from regorafenib, such as better performance status, disease that was responsive to prior therapies, and minimal comorbidities. Many studies have evaluated whether particular biomarkers have the potential to help select patients for regorafenib. To date, these investigations have not identified a particular biomarker of value.

H&O Do recent data suggest how to sequence or combine newer agents?

RG In the phase 3 RECURSE trial of trifluridine/tipiracil, previous use of regorafenib was reported in 27% of patients in Europe and 24.2% of patients in the United States.

Most studies have evaluated regorafenib as a single agent in later lines of therapy. At Ohio State University,

we are evaluating folinic acid, fluorouracil (5-FU), and irinotecan (FOLFIRI) plus regorafenib (administered one week on and one week off) in the second-line setting in a phase 2 trial. There are also studies of regorafenib in combination with oxaliplatin and other agents in earlier settings. In new drug development, the general approach is to first establish single-agent activity and then optimize use in combination therapy. How to use regorafenib in earlier treatment settings is not yet known. However, we are gaining experience, and clinical data are forthcoming. In the study at Ohio State University combining FOLFIRI plus regorafenib, the tolerance has been better than expected. The results so far suggest that regorafenib can be combined with cytotoxic chemotherapy without causing prohibitive toxicity.

H&O Do you have any recommendations regarding the clinical use of newer agents?

RG Regorafenib and TAS-102 both have activity in patients with refractory colon cancer, and they add to the treatment armamentarium. In colon cancer, patients often develop refractory disease before they have deteriorated, and they are still interested in active therapy. It is important to take advantage of agents approved in the refractory disease setting to increase patients' survival and sustain their quality of life.

Disclosure

Dr Goldberg's institution has received research support from Bayer. He is a paid consultant to Taiho.

Suggested Readings

ClinicalTrials.gov. First line treatment of metastatic colorectal cancer with mFOLFOX6 in combination with regorafenib. <https://clinicaltrials.gov/ct2/show/NCT01289821>. Identifier: NCT01289821. Accessed November 11, 2015.

ClinicalTrials.gov. Lower or standard dose regorafenib in treating patients with refractory metastatic colorectal cancer (ReDOS). Identifier: NCT02368886. <https://clinicaltrials.gov/ct2/show/NCT02368886>. Accessed December 3, 2015.

ClinicalTrials.gov. Regorafenib+FOLFIRI versus placebo+FOLFIRI as 2nd line tx in metastatic colorectal cancer. Identifier: NCT01298570. <https://clinicaltrials.gov/ct2/show/NCT01298570>. Accessed November 13, 2015.

Goldberg RM, Sargent DJ, Morton RF, et al. NCCTG Study N9741: leveraging learning from an NCI Cooperative Group phase III trial. *Oncologist*. 2009;14(10):970-978.

Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.

Li J, Qin S, Xu R, et al; CONCUR Investigators. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.

Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.

Van Cutsem E, Ciardiello F, Seitz J-F, et al. Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer [World GI Congress abstract LBA-05]. *Ann Oncol*. 2015;26(suppl 4).