

Multicenter, Randomized, Double-Blind Phase 2 Trial of FOLFIRI With Regorafenib or Placebo as Second-Line Therapy for Metastatic Colorectal Cancer

Hanna K. Sanoff, MD ¹; Richard M. Goldberg, MD^{2,3}; Anastasia Ivanova, PhD¹; Seamus O'Reilly, MD, PhD⁴; Samer S. Kasbari, MD⁵; Richard D. Kim, MD⁶; Ray McDermott, MD, PhD⁴; Dominic T. Moore, MS¹; William Zamboni, PhD¹; William Grogan, MD⁴; Allen Lee Cohn, MD⁷; Tanios S. Bekaii-Saab, MD^{2,8}; Gregory Leonard, MD⁴; Theresa Ryan, MD⁹; Olugbenga O. Olowokure, MD¹⁰; Nishan H. Fernando, MD¹¹; John McCaffrey, MD⁴; Bassel F. El-Rayes, MD ¹²; Anne M. Horgan, MD⁴; Gary Bradley Sherrill, MD¹³; George Hosni Yacoub, MD¹⁴; and Bert H. O'Neil, MD¹⁵

BACKGROUND: Regorafenib, a multikinase inhibitor that inhibits angiogenesis, growth, and proliferation, prolongs survival as monotherapy in patients with refractory colorectal cancer. This international, double-blind, placebo-controlled, multicenter trial assessed the efficacy of regorafenib with folinic acid, fluorouracil, and irinotecan (FOLFIRI) as a second-line treatment for metastatic colorectal cancer. **METHODS:** Patients with metastatic colorectal cancer who progressed on first-line oxaliplatin and fluoropyrimidine enrolled at 45 sites in the United States and Ireland. Patients, stratified by prior bevacizumab use, were randomized 2:1 to regorafenib or placebo. The treatment consisted of FOLFIRI on days 1 and 2 and days 15 and 16 with 160 mg of regorafenib or placebo on days 4 to 10 and days 18 to 24 of every 28-day cycle. Crossover was not allowed. The primary endpoint was progression-free survival (PFS). Under the assumption of a 75% event rate, 180 patients were required for 135 events to achieve 90% power to detect a hazard ratio (HR) of 0.65 with a 1-sided α value of .1. **RESULTS:** One hundred eighty-one patients were randomized (120 to regorafenib-FOLFIRI and 61 to placebo-FOLFIRI) with a median age of 62 years. Among these, 117 (65%) received prior bevacizumab or aflibercept. PFS was longer with regorafenib-FOLFIRI than placebo-FOLFIRI (median, 6.1 vs 5.3 months; HR, 0.73; 95% confidence interval [CI], 0.53-1.01; log-rank $P=.056$). The median overall survival was not longer (HR, 1.01; 95% CI, 0.71-1.44). The response rate was higher with regorafenib-FOLFIRI (34%; 95% CI, 25%-44%) than placebo-FOLFIRI (21%; 95% CI, 11%-33%; $P=.07$). Grade 3/4 adverse events with a >5% absolute increase from regorafenib included diarrhea, neutropenia, febrile neutropenia, hypophosphatemia, and hypertension. **CONCLUSIONS:** The addition of regorafenib to FOLFIRI as second-line therapy for metastatic colorectal cancer only modestly prolonged PFS over FOLFIRI alone. *Cancer* 2018;124:3118-26. © 2018 American Cancer Society.

KEYWORDS: angiogenesis inhibitor, chemotherapy, colorectal cancer, tyrosine kinase inhibitor.

INTRODUCTION

Colorectal cancer remains a major global health problem with an estimated 1.4 million new cases and 700,000 deaths worldwide.¹ With the advent of multiple new drugs in the last decade, the life expectancy of patients with metastatic colorectal cancer has markedly improved and is now frequently reported to be longer than 30 months.²⁻⁴ This prolonged duration of disease control comes from a long continuum of cancer treatment, whereby patients are typically treated with sequential combination chemotherapy as both first- and second-line treatments. However, the median survival from the start of second-line combination chemotherapy in multiple trials has been approximately 1 year, and progression-free survival (PFS) is commonly around 5 months. There is clearly an unmet need for improved second-line therapy.⁵

The addition of antibody-based inhibitors of angiogenesis (bevacizumab, aflibercept, and ramucirumab) or epidermal growth factor receptor (EGFR; cetuximab and panitumumab) to second-line chemotherapy prolongs PFS and overall survival (OS) in comparison with chemotherapy alone.⁵⁻⁹ However, the benefit of EGFR inhibitors is confined to the approximately 45% of patients with all-*RAS* wild-type tumors,¹⁰ and the incremental benefit of the 3 monoclonal antibodies against the vascular endothelial growth factor pathway over chemotherapy is modest.

Corresponding author: Hanna K. Sanoff, MD, Division of Hematology/Oncology, University of North Carolina, 170 Manning Drive, Chapel Hill, NC 27599; hanna_sanoff@med.unc.edu

¹Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; ²Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital, Columbus, Ohio; ³West Virginia University, Morgantown, West Virginia; ⁴Cancer Trials Ireland, Dublin, Ireland; ⁵Southeastern Medical Oncology Center, Goldsboro, North Carolina; ⁶H. Lee Moffitt Cancer Center, Tampa, Florida; ⁷Rocky Mountain Cancer Center, Denver, Colorado; ⁸Division of Hematology/Oncology, Mayo Clinic, Phoenix, Arizona; ⁹New York University Langone Medical Center, New York, New York; ¹⁰University of Cincinnati, Cincinnati, Ohio; ¹¹Georgia Cancer Specialists, Atlanta, Georgia; ¹²Winship Cancer Institute of Emory University, Atlanta, Georgia; ¹³Moses Cone Regional Cancer Center, Greensboro, North Carolina; ¹⁴Wake Forest University, Winston Salem, North Carolina; ¹⁵Indiana University, Indianapolis, Indiana

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Regorafenib is an oral, multitargeted kinase inhibitor with activity against mediators of angiogenesis (vascular endothelial growth factor receptor 1 [VEGFR1], VEGFR2, VEGFR3, and tyrosine kinase with immunoglobulin-like and EGF-like domains 2 [TIE2]), pro-oncogenic signaling (platelet-derived growth factor receptor β and fibroblast growth factor receptor [FGFR]), and growth and proliferation (BRAF, KIT, and RET). Regorafenib has been shown to prolong survival among patients with chemotherapy-refractory colorectal cancer, with similar benefits among patients with *RAS* mutations as with all wild-type cancers.^{11,12}

In this randomized, double-blind, placebo-controlled phase 2 study, we sought to evaluate whether the addition of regorafenib to second-line chemotherapy with folinic acid, fluorouracil, and irinotecan (FOLFIRI) would prolong PFS over FOLFIRI alone among patients with metastatic colorectal cancer who had progressed on a first-line combination regimen containing oxaliplatin and a fluoropyrimidine.

MATERIALS AND METHODS

Study Design

This randomized, double-blind, placebo-controlled trial was performed at 45 academic and community oncology practices in the United States and Ireland. The protocol was approved by the local institutional review board at each institution, and each patient gave written informed consent before participation. The trial was registered with ClinicalTrials.gov (NCT01298570).

Patients

Patients with unresectable metastatic colorectal cancer who had progressed on first-line therapy with oxaliplatin and 5-fluorouracil (5-FU) or capecitabine (with or without a prior biologic) were recruited. Patients were eligible if their disease had progressed during or within 6 months of first-line chemotherapy or if they had developed recurrent, metastatic disease within 9 months of completing adjuvant oxaliplatin-based chemotherapy for stage II or III cancer. Prior use of a biologic agent was permitted but not required. Additional key eligibility criteria included an age ≥ 18 years, an Eastern Cooperative Oncology Group performance status of 0 to 1, Response Evaluation Criteria in Solid Tumors—measurable disease, a life expectancy of at least 3 months, and adequate organ function. Patients were excluded from participation if any of the following applied: prior treatment with regorafenib; more than 1 prior chemotherapy for metastatic colorectal cancer, including prior treatment with irinotecan; poorly

controlled hypertension; arterial thrombotic events within 6 months; an inability to swallow pills; malabsorptive conditions; and active, untreated brain metastases.

Randomization and Masking

Consenting patients were randomized within each stratum with a constrained block randomization procedure¹³ with a maximum imbalance of 2; a 2:1 ratio in favor of the regorafenib treatment arm was used. A 2:1 ratio was selected to enhance patient enrollment. Treatment assignments were made by the coordinating center at the University of North Carolina at Chapel Hill. All participating investigators, study staff, and participants were blinded to the treatment assignment for the duration of the on-treatment period. After progression, unblinding was permitted if requested by the treating investigator. Unblinding was done by the study safety officer. Study staff at the coordinating site, including the principal investigator, remained blinded to the treatment arm until the date of unblinding, which was February 9, 2016.

Procedures

Treatment consisted of FOLFIRI (irinotecan at 180 mg/m², leucovorin at 400 mg/m², and 5-FU at 400 mg/m² [bolus] followed by 2400 mg/m² over 46 hours) on days 1 and 2 and days 15 and 16 plus regorafenib/placebo at 160 mg by mouth daily on days 4 to 10 and days 18 to 24 of every 28-day cycle. This regorafenib schedule was selected to minimize the overlap of toxic effects of regorafenib and chemotherapy.¹⁴ Treatment was continued until the time of tumor progression or unacceptable toxicity. Patients for whom it was clinically appropriate to discontinue one of the agents because of toxicity continued on the study treatment if either irinotecan or 5-FU was continued. No crossover to regorafenib was provided after progression on placebo; however, postprogression therapy was not dictated or restricted per protocol.

The tumor response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors 1.1 every 8 weeks until disease progression. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) throughout the study, with study visits performed on days 1 and 15 of cycle 1 and then monthly thereafter.

Data on local results of *KRAS*, *NRAS*, and *BRAF* mutations were obtained from sites. Central confirmatory testing is ongoing.

A pharmacokinetic substudy was conducted at selected sites to determine the effect of regorafenib on the

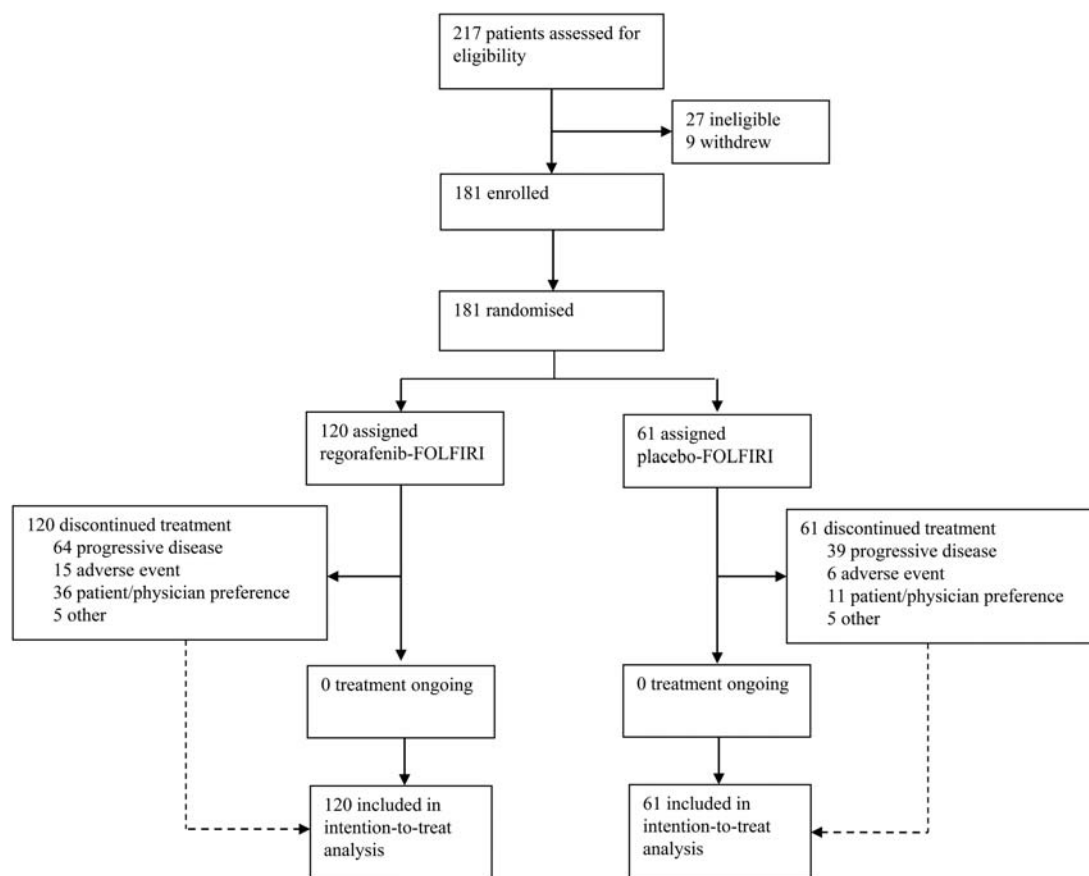


Figure 1. Consolidated Standards of Reporting Trials diagram. FOLFIRI indicates folinic acid, fluorouracil, and irinotecan.

pharmacokinetics of irinotecan and its active metabolite SN-38. In participating patients, blood was drawn at the following time points with respect to the irinotecan infusion on day 1 of cycles 1 and 2: predose; start plus 1 hour; end; end plus 15, 30, and 45 minutes; and end plus 1, 2, 4, 5, and 24 hours. Regorafenib dosing began as planned on day 4.

Outcomes

The primary endpoint of the study was PFS from the date of randomization to the time of investigator-assessed progression or death. Secondary endpoints included the radiographic response rate, disease control rate (complete responses plus partial responses plus stable disease), rates of grade 3 to 5 adverse events, effect of regorafenib on irinotecan pharmacokinetics, and OS.

Statistical Analysis

With 135 events, this study had 90% power to detect a 60% improvement in PFS in the regorafenib-FOLFIRI arm versus the placebo-FOLFIRI arm; this corresponded to a target hazard ratio (HR) of 0.65 (log-rank test) and a

1-sided α level of .10 (eg, statistical significance was set a priori at $<.1$). A sample size of 180 patients was selected to observe 135 events because of the expected accrual rate and the average length of follow-up.

The Kaplan-Meier (or product-limit) method was used to estimate the time-to-event functions of PFS and OS. PFS was defined as the time from the date of randomization to disease progression or death (whichever occurred first) or the date of last contact. OS was defined as the time from the date of randomization to the date of death or the date of last contact. Efficacy analyses were conducted for all randomized patients as an intent-to-treat analysis. For the primary analysis, an unstratified log-rank test was used to test for differences between treatment arms in the time-to-event analyses. In the sensitivity analysis, a log-rank test stratified on prior bevacizumab use was performed. Because there was no substantive difference in these results, the unstratified results are presented. Because this was a double-blinded study, the intention-to-treat PFS and OS analyses censored all patients who had not had an event by the unblinding date of February 9, 2016.

TABLE 1. Patient Characteristics by Treatment Arm

| Characteristic | Regorafenib-FOLFIRI (n = 120) | Placebo-FOLFIRI (n = 61) |
|--------------------------------------|----------------------------------|-----------------------------|
| Age, median (range), y | 62 (30-94) | 62 (30-82) |
| Sex, No. (%) | | |
| Female | 52 (43) | 29 (48) |
| Male | 68 (57) | 30 (52) |
| Race, No. (%) | | |
| White | 99 (83) | 48 (81) |
| Black | 20 (17) | 11 (19) |
| Latino, No. (%) | 4 (3) | 2 (3) |
| Country, No. (%) | | |
| United States | 84 (70) | 43 (70) |
| Ireland | 36 (30) | 18 (30) |
| ECOG PS, No. (%) | | |
| 0 | 52 (43) | 23 (38) |
| 1 | 68 (57) | 38 (62) |
| Baseline comorbidity, No. (%) | | |
| Hypertension | 47 (36) | 26 (41) |
| DVT or PE | 9 (7) | 3 (5) |
| CAD | 4 (3) | 3 (5) |
| Metastatic at diagnosis, No. (%) | 86 (72) | 46 (75) |
| Prior biologic agent, No. (%) | | |
| None | 33 (28) | 16 (26) |
| Bevacizumab/aflibercept ^a | 76 (63) | 41 (67) |
| Cetuximab/panitumumab | 11 (9) | 4 (7) |
| Locally reported RAS, No. (%) | | |
| Wild type | 49 (41) | 18 (30) |
| Mutated | 54 (45) | 37 (61) |
| Unknown | 17 (14) | 6 (9) |

Abbreviations: CAD, coronary artery disease; DVT, deep venous thrombosis; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid, fluorouracil, and irinotecan; PE, pulmonary embolus; PS, performance status.

^aThree patients in the placebo arm received prior aflibercept. All others received bevacizumab.

A post hoc exploratory analysis of the effect of regorafenib on PFS in clinically relevant subgroups was performed with multivariate Cox proportional hazards models. Because of the small sample size of each subgroup and the hypothesis-generating nature of this analysis, formal interaction testing was not performed.

The radiological response rates and disease control rates are reported as percentages along with their exact 95% confidence intervals (CIs). Fisher's exact test was used to compare these rates in the intention-to-treat population as well as the evaluable population of patients who completed their first per-protocol imaging. The effect of regorafenib on irinotecan and SN-38 pharmacokinetics was evaluated through the comparison of the paired differences between the mean areas under the curve (AUCs) of cycles 1 and 2 with the Wilcoxon sign-rank test, and the comparison of the difference between treatment arms was performed with the Wilcoxon 2-group test. Safety

was assessed by the evaluation of the frequency tables of grade 3 to 5 toxicities thought to be related to treatment in patients receiving at least 1 dose of the study drug. Statistical tests for all secondary outcomes were 2-sided. Statistical analyses were performed with SAS statistical software (version 9.4; SAS Institute, Inc, Cary, North Carolina) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

RESULTS

A total of 181 patients—120 regorafenib-FOLFIRI patients and 61 placebo-FOLFIRI patients—were randomized between April 2011 and August 2015 (Fig. 1). The study population had a median age of 62 years (range, 30-94 years; Table 1). Prior bevacizumab or aflibercept had been administered to 76 of the regorafenib-FOLFIRI patients (63%) and to 41 of the placebo-FOLFIRI patients (67%). Only 15 patients were exposed to an EGFR inhibitor in the first line (11 regorafenib patients and 4 placebo patients).

The median PFS of patients treated with regorafenib-FOLFIRI (6.1 months; 95% CI, 5.5-7.3 months) was longer than that of patients treated with placebo-FOLFIRI (5.3 months; 95% CI, 4.1-6.0 months) with an HR for PFS of 0.73 (95% CI, 0.53-1.01; $P = .056$; Fig. 2A). We performed several unplanned subgroup analyses. Because of the small sample, all estimates had wide CIs; however, there was no suggestion from the efficacy point estimates that the benefit of regorafenib for PFS was attenuated in patients 70 years old or older (HR, 0.51; 95% CI, 0.25-1.02), in patients with a worse performance status (HR, 0.73; 95% CI, 0.48-1.10), in patients with *RAS* mutations (HR, 0.72; 95% CI, 0.46-1.12), or in those with prior angiogenesis inhibitor use (HR, 0.69; 95% CI, 0.47-1.02; Fig. 3).

The intention-to-treat response rate was numerically higher in the regorafenib-FOLFIRI arm (29%; 95% CI, 21%-38%) than the placebo-FOLFIRI arm (20%; 95% CI, 11%-32%; $P = .21$). No patient had a complete radiographic response. In the subset of evaluable patients (those who had completed at least 1 restaging scan), the response rate was higher among the 102 regorafenib-FOLFIRI-treated patients (34%; 95% CI, 25%-44%) than the 58 placebo-FOLFIRI-treated patients (21%; 95% CI, 11%-33%; $P = .07$), as was the disease control rate (82% [95% CI, 74%-89%] vs 74% [95% CI, 61%-85%]; $P = .23$).

At the time of the data lock, 92 regorafenib-FOLFIRI patients and 46 placebo-FOLFIRI patients had

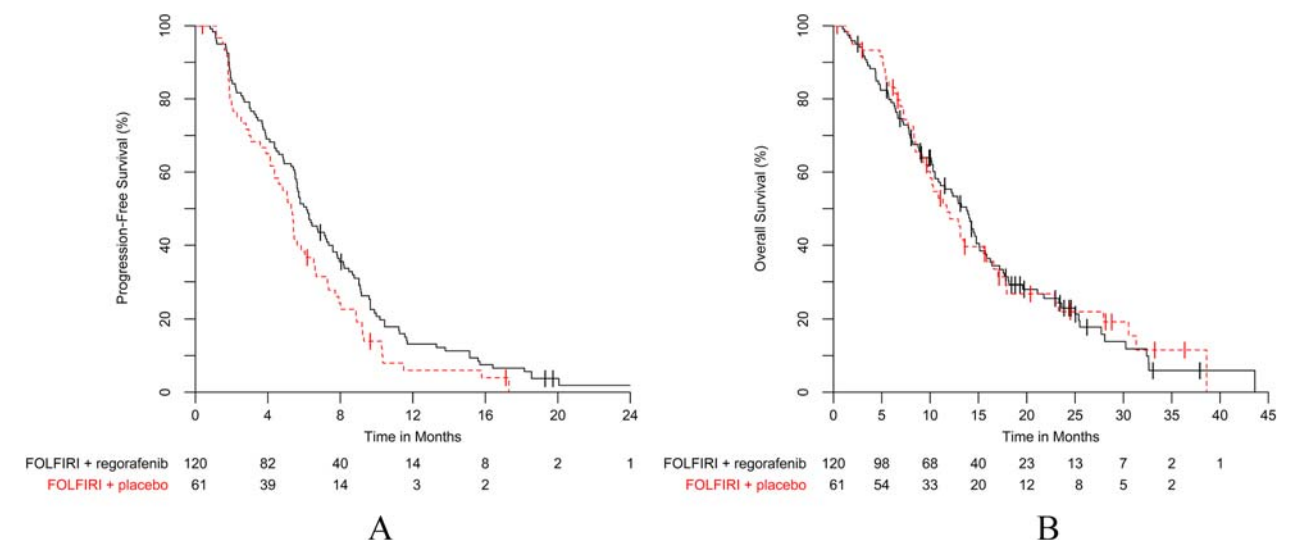


Figure 2. Kaplan-Meier analysis: (A) progression-free survival and (B) overall survival. FOLFIRI indicates folinic acid, fluorouracil, and irinotecan.

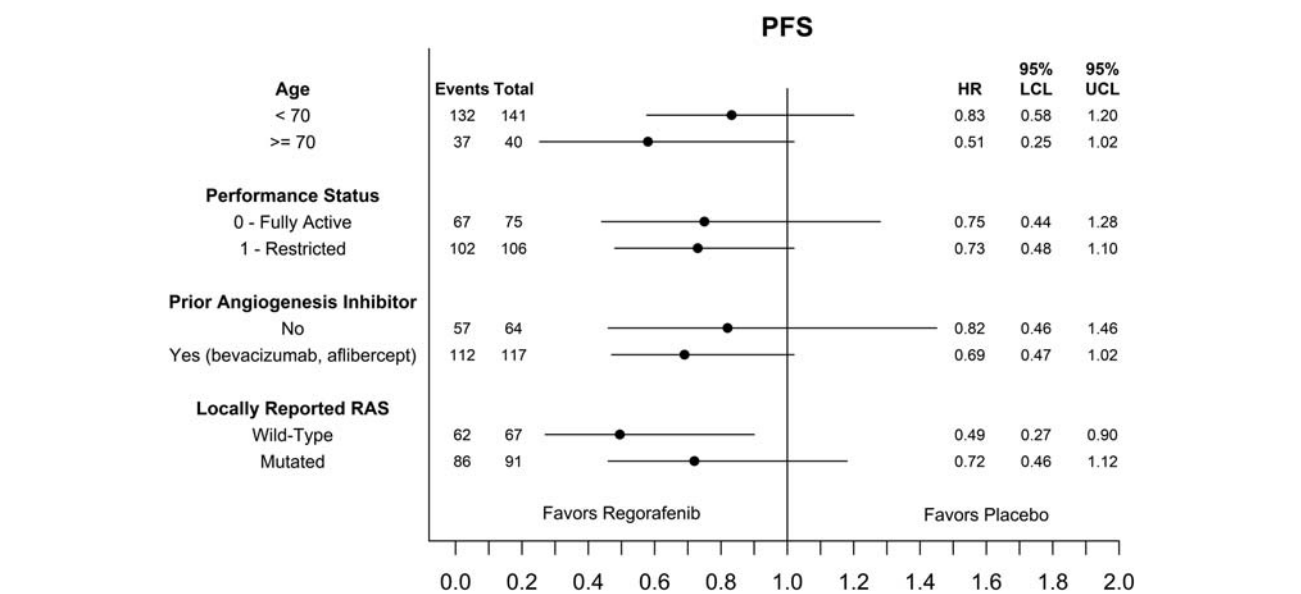


Figure 3. Subgroup analysis of PFS by key characteristics. HR indicates hazard ratio; LCL, lower confidence limit; PFS, progression-free survival; UCL, upper confidence limit.

died. The median OS was numerically but not statistically longer for regorafenib-FOLFIRI-treated patients (13.8 months; 95% CI, 10.5-14.8 months) versus placebo-FOLFIRI-treated patients (11.7 months; 95% CI, 8.9-15.8 months; HR, 1.01; 95% CI, 0.71-1.44; $P = .94$; Fig. 2B).

Twenty-two patients (11 regorafenib patients and 11 placebo patients) participated in the pharmacokinetic substudy. The median AUC of SN-38 (the active

metabolite of irinotecan) did not significantly change in the regorafenib-FOLFIRI arm from cycle 1 (0.68 ng/mL h; interquartile range, 0.49-0.89 ng/mL h) to cycle 2 (0.59 ng/mL h; interquartile range, 0.24-0.85 ng/mL h; $P = .47$). Furthermore, there was no significant difference between the SN-38 dose-normalized plasma AUC ratio of cycle 1 to cycle 2 between arms, and this suggests that regorafenib does not alter irinotecan pharmacokinetics.

TABLE 2. Drug-Related Treatment Emergent Adverse Events

| Event | Regorafenib-FOLFIRI (n = 120), No. (%) | | | Placebo-FOLFIRI (n = 61), No. (%) | |
|-----------------------------------|---|---------|---------|--------------------------------------|---------|
| | Grade 3 | Grade 4 | Grade 5 | Grade 3 | Grade 4 |
| Anemia | 4 (3) | 1 (1) | 0 | 4 (7) | 0 |
| Anorexia | 6 (5) | 0 | 0 | 0 | 0 |
| Dehydration | 7 (6) | 0 | 0 | 2 (3) | 0 |
| Diarrhea | 16 (13) | 2 (2) | 0 | 2 (3) | 1 (2) |
| Fatigue | 13 (11) | NA | NA | 4 (7) | NA |
| Febrile neutropenia | 9 (8) | 2 (2) | 0 | 2 (3) | 0 |
| Hypertension | 10 (8) | 0 | 0 | 1 (2) | 0 |
| Hypokalemia | 5 (4) | 2 (2) | 0 | 1 (2) | 0 |
| Hypophosphatemia | 17 (14) | 0 | 0 | 0 | 0 |
| Lipase increase | 7 (6) | 3 (3) | NA | 3 (5) | 0 |
| Mucositis | 10 (8) | 1 (1) | 0 | 6 (10) | 0 |
| Neutropenia | 26 (22) | 23 (19) | NA | 12 (20) | 6 (10) |
| Palmar-plantar erythrodysesthesia | 6 (5) | NA | NA | 1 (2) | NA |
| Rectal hemorrhage | 0 | 0 | 1 (1) | 0 | 0 |
| Thrombocytopenia | 3 (3) | 2 (2) | NA | 0 | 0 |
| Thromboembolism | 6 (5) | 0 | 0 | 1 (2) | 0 |
| Leukopenia | 9 (8) | 2 (2) | NA | 6 (10) | 1 (2) |

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; NA, not applicable (no grade 4 or 5 for the given adverse event).

The worst grade per patient is shown for adverse events deemed to be at least possibly related to treatment and occurring in more than 5% of patients in either arm (or any grade 5 toxicity).

Patients received a median of 4 cycles (range, 1-30 cycles) of regorafenib-FOLFIRI and 4 cycles (range, 1-16 cycles) of placebo-FOLFIRI. Reasons for treatment discontinuation for regorafenib-FOLFIRI and placebo-FOLFIRI were progression (53% vs 64%), toxicity (12% vs 10%), patient/physician preference due to a low-grade toxicity not requiring discontinuation per protocol (14% vs 7%), and other patient/physician preference (16% vs 11%). Three patients in the regorafenib-FOLFIRI arm and 1 patient in the placebo-FOLFIRI arm withdrew to undergo surgical resection. Regorafenib/placebo dose reductions were required in more patients in the regorafenib arm (70 [58%]) than the placebo arm (15 [25%]). Also, more patients in the regorafenib-FOLFIRI arm required dose reductions in 5-FU (80 [66%]) or irinotecan (80 [66%]) than patients in the placebo-FOLFIRI arm (20 [33%] and 18 [30%], respectively).

More patients experienced severe (grade 3 or higher) toxicity in the regorafenib-FOLFIRI arm (95/120 or 79%) than the placebo-FOLFIRI arm (36 of 61 or 59%; $P = .005$); this included increased rates of neutropenia (41% vs 30%), febrile neutropenia (10% vs 3%), diarrhea (15% vs 5%), hypophosphatemia (14% vs 0%), hypertension (8% vs 2%), and elevated lipase (8% vs 3%; Table 2). On this intermittent dosing schedule, grade 3 hand-foot syndrome occurred in only 6 of the regorafenib-treated patients (5%).

After progression, 31% of the patients in each arm received no further therapy. Patients in the regorafenib-FOLFIRI arm received subsequent therapy less commonly, with 47 (39%) receiving 1 additional line of therapy and 25 (21%) receiving 2 or more postprogression lines (Table 3). In comparison, 15 of the placebo-FOLFIRI patients (25%) received only 1 line, and 20 (33%) received 2 or more lines of subsequent therapy. Ten placebo-FOLFIRI patients (16%) went on to receive postprogression regorafenib, whereas 8 of the regorafenib-FOLFIRI patients (7%) did.

DISCUSSION

This multicenter, double-blind, placebo-controlled study demonstrated that the addition of the multikinase inhibitor regorafenib to FOLFIRI resulted in a 27% relative reduction in progression or death in comparison with FOLFIRI alone as second-line therapy for metastatic colorectal cancer. Because the level of statistical significance for this phase 2 trial was set at .1, the trial met its primary endpoint for PFS; however, the corresponding absolute improvement in median survival was only 0.8 months, and this did not translate into a benefit in survival. With the improvement in PFS, the 13% absolute increase in the radiographic response rate in regorafenib-treated patients lends further support for the increased clinical activity of the regorafenib-FOLFIRI combination over chemotherapy alone; however, it is tempered by the increase in

TABLE 3. Subsequent Therapy

| | Regorafenib-FOLFIRI (n = 120), No. (%) | Placebo-FOLFIRI (n = 61), No. (%) |
|----------------------------|---|--------------------------------------|
| Unavailable | 11 (9) | 7 (11) |
| None | 37 (31) | 19 (31) |
| 1 additional line | 47 (39) | 15 (25) |
| ≥2 additional lines | 25 (21) | 20 (33) |
| Specific agents used | | |
| Regorafenib | 8 (7) | 10 (16) |
| Cetuximab or panitumumab | 22 (18) | 13 (21) |
| Bevacizumab | 26 (22) | 17 (28) |
| Aflibercept or ramucirumab | 6 (5) | 2 (3) |
| Oxaliplatin | 14 (12) | 12 (20) |
| Irinotecan | 41 (34) | 19 (31) |
| 5-FU or capecitabine | 53 (44) | 23 (38) |
| Trifluridine-tipiracil | 4 (3) | 1 (2) |
| Clinical trial | 7 (6) | 4 (7) |
| Other | 3 (2) | 3 (5) |

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRI, folinic acid, fluorouracil, and irinotecan.

moderate and severe toxicity, which led to dose reductions of regorafenib in 58% and of FOLFIRI in 66% of treated patients. These dose reductions may in part explain the lack of an OS benefit from combination therapy.

The relative reduction in the risk of progression or death from the addition of regorafenib to FOLFIRI in this trial is qualitatively similar to the benefits seen in recently published trials of angiogenesis inhibition (eg, bevacizumab, aflibercept, and ramucirumab) combined with chemotherapy in populations unselected by *RAS*⁶⁻⁸ and of EGFR inhibition (panitumumab) combined with chemotherapy in *RAS* wild-type cancers.⁵ The overall response rate in this trial, however, was quite high at 34% in the regorafenib arm. The estimate is comparable to the response rate seen with the addition of panitumumab to FOLFIRI (35%)⁵ and is considerably higher than the rates with the addition of angiogenesis inhibitors to chemotherapy (6% with bevacizumab, 19% with aflibercept, and 13% with ramucirumab).⁶⁻⁸ Notably, the response rate in the placebo-FOLFIRI arm of this trial was also higher than those seen in the aforementioned phase 3 trials using a FOLFIRI backbone, which had rates ranging from 10% to 12.5% versus the rate of 20% in our intention-to-treat population. In our study, response and progression were not confirmed centrally.

Although OS was numerically longer, regorafenib did not significantly prolong OS in this trial. At the time of unblinding, only 138 events had occurred, and this rendered this trial underpowered to detect a difference in survival. However, in a post hoc exploratory analysis including events that occurred after unblinding with censoring at last contact,

there was no greater trend toward a survival benefit (HR, 1.01; 95% CI, 0.72-1.40; log-rank *P* = .97). Postprogression survival may have been influenced by subsequent therapies, which were received by 69% of the patients.

This trial was designed before the presentation of the ML18147 data, which demonstrated a small survival benefit from bevacizumab with combination chemotherapy as second-line therapy.⁶ When these data were released, we convened an investigator meeting at which the majority of the investigators confirmed that they were still willing to enroll patients into this blinded, placebo-controlled trial because the benefit of bevacizumab in the second line was small. However, it seems likely that the use of a placebo arm slowed enrollment because of the 4-year accrual period. The availability of another second-line biologic option may also have influenced investigators' decision to remove patients from the protocol treatment in the absence of severe toxicity or progression; indeed, 26% of the patients stopped therapy because of preference.

Even with the intermittent regorafenib dosing schedule used in this trial in an attempt to thwart overlapping toxicity, 79% of regorafenib-FOLFIRI patients experienced grade 3 to 5 toxicity; this was a 20% absolute increase in severe toxicity in comparison with the placebo arm. Although this is comparable to the absolute increase in severe toxicity seen in recent combination studies of FOLFIRI with panitumumab, aflibercept, and ramucirumab (15%-21% absolute increases),^{5,7,8} two-thirds of the patients in the regorafenib arm required a dose reduction of FOLFIRI. This toxicity did not appear to be the result of a drug interaction because in our small pharmacokinetic sub-study there was no increase in the dose-adjusted AUC of either irinotecan or SN-38 from cycle 1 to cycle 2 in regorafenib-treated patients; in fact, both actually had a nonsignificant decrease. In contrast, a prior study using this same dosing schedule reported an increase in the SN-38 AUC from cycle 1 to 2, although it had a similar rate (65%) of dose reduction of FOLFIRI.¹⁴ The reason for the discrepancy in the SN-38 AUC is uncertain, and it may well be due to chance because of the small number of studied patients in each report. Using a continuous dosing schedule, a small observational study reported similar grade 3 or higher adverse events in 71%, though with higher incidences of severe hand-foot syndrome (61%) and mucositis (38%).¹⁵ Together, these studies all suggest full-dose FOLFIRI and regorafenib, even on an intermittent schedule, are not tolerable for most patients. Certainly, the need for dose reduction and higher rates of discontinuation for toxicity in the regorafenib arm of our study likely explain why, despite increased clinical activity as evidenced by the higher

response rate, there was only a small effect on PFS as well as no survival benefit from the addition of regorafenib.

In summary, the addition of regorafenib to FOLFIRI increases its clinical efficacy as second-line therapy for metastatic colorectal cancer. The added toxicity cost from this combination leads to frequent dose reductions, which likely account for the lack of an OS benefit. With little clinical activity seen with the combination of regorafenib with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) in the first line,¹⁶ regimens combining regorafenib with FOLFOX or FOLFIRI are unlikely to provide clinically meaningful improvements for patients with metastatic colorectal cancer.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Hanna K. Sanoff: Conception and design, patient recruitment and data acquisition, data interpretation, drafting of the manuscript, critical review of the manuscript, and final approval. **Richard M. Goldberg:** Conception and design, patient recruitment and data acquisition, data interpretation, critical review of the manuscript, and final approval. **Anastasia Ivanova:** Conception and design, data analysis, data interpretation, critical review of the manuscript, and final approval. **Seamus O'Reilly:** Patient recruitment and data acquisition, critical review of the manuscript, and final approval. **Samer S. Kasbari:** Patient recruitment and data acquisition, critical review of the manuscript, and final approval. **Richard D. Kim:** Patient recruitment and data acquisition, critical review of the manuscript, and final approval. **Ray McDermott:** Patient recruitment and data acquisition, critical review of the manuscript, and final approval. **Dominic T. Moore:** Conception and design, data analysis, data interpretation, critical review of the manuscript, and final

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