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Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With *KRAS* Wild-Type Advanced or Metastatic Colorectal Cancer
A Randomized Clinical Trial

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IMPORTANCE Combining biologic monoclonal antibodies with chemotherapeutic cytotoxic drugs provides clinical benefit to patients with advanced or metastatic colorectal cancer, but the optimal choice of the initial biologic therapy in previously untreated patients is unknown.

OBJECTIVE To determine if the addition of cetuximab vs bevacizumab to the combination of leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6) regimen or the combination of leucovorin, fluorouracil, and irinotecan (FOLFIRI) regimen is superior as first-line therapy in advanced or metastatic *KRAS* wild-type (wt) colorectal cancer.

DESIGN, SETTING, AND PARTICIPANTS Patients (≥18 years) enrolled at community and academic centers throughout the National Clinical Trials Network in the United States and Canada (November 2005-March 2012) with previously untreated advanced or metastatic colorectal cancer whose tumors were *KRAS* wt chose to take either the mFOLFOX6 regimen or the FOLFIRI regimen as chemotherapy and were randomized to receive either cetuximab (n = 578) or bevacizumab (n = 559). The last date of follow-up was December 15, 2015.

INTERVENTIONS Cetuximab vs bevacizumab combined with either mFOLFOX6 or FOLFIRI chemotherapy regimen chosen by the treating physician and patient.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival. Secondary objectives included progression-free survival and overall response rate, site-reported confirmed or unconfirmed complete or partial response.

RESULTS Among 1137 patients (median age, 59 years; 440 [39%] women), 1074 (94%) of patients met eligibility criteria. As of December 15, 2015, median follow-up for 263 surviving patients was 47.4 months (range, 0-110.7 months), and 82% of patients (938 of 1137) experienced disease progression. The median overall survival was 30.0 months in the cetuximab-chemotherapy group and 29.0 months in the bevacizumab-chemotherapy group with a stratified hazard ratio (HR) of 0.88 (95% CI, 0.77-1.01; *P* = .08). The median progression-free survival was 10.5 months in the cetuximab-chemotherapy group and 10.6 months in the bevacizumab-chemotherapy group with a stratified HR of 0.95 (95% CI, 0.84-1.08; *P* = .45). Response rates were not significantly different, 59.6% vs 55.2% for cetuximab and bevacizumab, respectively (difference, 4.4%, 95% CI, 1.0%-9.0%, *P* = .13).

CONCLUSIONS AND RELEVANCE Among patients with *KRAS* wt untreated advanced or metastatic colorectal cancer, there was no significant difference in overall survival between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment.

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Supplemental content

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Colorectal cancer is the second leading cause of cancer death in North America. Fluorouracil became the only cytotoxic drug indicated for colorectal cancer in the 1990s[1] when the adoption of continuous infusion of this agent was found to have improved the median overall survival from 12 to 15 months.[2] Since then, combination therapies of fluorouracil with leucovorin and either irinotecan (FOLFIRI regimen[3]) or oxaliplatin (mFOLFOX6 regimen[4]) were found to further improve survival and have become the main chemotherapeutic treatment options for colorectal cancer. A randomized crossover trial showed that these combination regimens were not statistically different, with patients receiving these agents in any sequence surviving a median 18 to 20 months.[5,6]

Cetuximab, a chimerized monoclonal antibody to the epidermal growth factor receptor (EGFR), was approved in combination with irinotecan or alone following irinotecan failure for patients with advanced or metastatic colorectal cancer whose tumors expressed EGFR.[7] Subsequent evidence indicated that cetuximab activity was unrelated to tumor expression of EGFR.[8] Bevacizumab, a humanized murine antihuman vascular endothelial growth factor (VEGF) monoclonal antibody, was then approved for patients with advanced colorectal cancer in combination with fluorouracil-based chemotherapy.[9] The addition of cetuximab or bevacizumab to cytotoxic chemotherapeutic combinations proved feasible and appeared to be more active than cytotoxic chemotherapies alone.[10] These new options for patients with advanced or metastatic colorectal cancer raised the question of which was the optimal biologic monoclonal antibody-chemotherapy combination.

This trial was conducted to determine if the addition of cetuximab vs bevacizumab to the mFOLFOX6 regimen or the FOLFIRI regimen was superior as first-line therapy in advanced or metastatic *KRAS* wild-type (wt) colorectal cancer.

Key Points

Question Does the addition of cetuximab with a combination chemotherapeutic regimen improve overall survival compared with the addition of bevacizumab with a combination chemotherapeutic regimen as the initial treatment for patients with advanced or metastatic colorectal cancer who have *KRAS* wild-type tumors?

Findings In this randomized clinical trial involving 1137 patients, there was no significant difference in overall survival among patients treated with either leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6) or leucovorin, fluorouracil, and irinotecan (FOLFIRI) and then randomized to receive cetuximab or bevacizumab.

Meaning Neither biologic monoclonal antibody demonstrated significantly greater overall survival for initial treatment of advanced or metastatic colorectal cancer.

Methods

The Cancer and Leukemia B and Southwest Oncology Group 80405 trial was designed in collaboration with the National Cancer Institute (NCI) and was started in September 2005 to compare various combinations of chemotherapies and biologic therapies as first-line treatment of advanced and metastatic colorectal cancer: (1) chemotherapies plus cetuximab; (2) chemotherapies plus bevacizumab; and (3) chemotherapies plus cetuximab and bevacizumab (The study protocol is available in Supplement 1). Within 3 years, the lack of efficacy of EGFR antibodies in *KRAS*-mutant tumors[11] and failures of the dual antibody and chemotherapy combination treatments[12,13] resulted in a pivotal amendment restricting eligibility to patients with confirmed *KRAS* wt tumors and then later to closure of the dual antibody group. After 10 years and additional amendments a revised 2-group trial (cetuximab vs bevacizumab with chemotherapy regimens) completed patient enrollment and follow-up (see eTable 1 in Supplement 2).

In 2010, the Cancer and Leukemia B group became a part of the Alliance for Clinical Trials in Oncology (Alliance). This cooperative research group performed critical aspects of the present study: (1) captured the clinical data; (2) performed all statistical analyses; (3) provided data and safety monitoring for toxicity and for preplanned interim efficacy analyses. The Southwest Oncology Group partner for the present study oversaw specimen biobanking and the distribution of samples to laboratory investigators.

Patient Eligibility

Institutional review board approval was required at all participating centers and all participating patients provided written informed consent. Patients were enrolled at centers across the National Cancer Trials Network in the United States and Canada. Eligible patients had pathology-documented untreated locally advanced or metastatic colorectal cancer, although measurable disease (tumor that could be quantified) was not require. Patients had to be candidates for either mFOLFOX6 or FOLFIRI regimens without known central nervous system metastases or grade II or greater peripheral neuropathy. In addition, hypertension had to be well controlled (blood pressure <160/90 mm Hg with treatment) and there could be no concurrent congestive heart failure. Therapeutic anticoagulation was permitted as long as the patient was therapeutic on a stable dose of anticoagulant. Patients with a significant bleeding event within 6 months of enrollment or a gastrointestinal perforation within 12 months of enrollment were excluded unless the perforated bowel segment had been resected. Up to 6 months of prior adjuvant treatment had to have concluded at least 12 months before recurrence. Prior radiotherapy to 5040 cGy was allowed but could not have encompassed more than 25% of bone marrow. Patients were excluded if they had undergone major surgery within the last 4 weeks or minor surgery within the last 2 weeks.

National Cancer Institute trials are required to capture and report data on race/ethnicity. Data for patient covariates were captured in the NCI-standardized format and entered at the time of patient registration usually by a clinical research associate at the treating institution. Race/ethnicity was determined by self-report.

Patients were 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 to 1 and normal hepatic, renal, and hematologic laboratory values. Initially, enrolled patients could consent to the biomarker companion study (Cancer and Leukemia Group B 150506) and submit a specimen for EGFR status evaluation. In November 2008, *KRAS* wt (codons 12 and 13) became an eligibility criterion. In September 2009, the combined treatment group of both cetuximab and bevacizumab with chemotherapeutic regimen was discontinued. Patients in that treatment group were removed from the study, received treatment at the discretion of their physician, and were followed up per protocol. Patients enrolled and consented to the companion study whose tumor was *KRAS* wt and who received single antibody treatment were included in the primary cohort. Patients with *KRAS* mutant tumors were excluded from analysis but were given the option to continue taking the study treatment.

Following the amendment restricting eligibility to patients with *KRAS* wt tumors, patients consented to be tested for *KRAS* and agreed to submit 2 archival paraffin-embedded tumor tissue sections and 1 histology reference slide or 1 paraffin-embedded tumor block to the Southwest Oncology Group Solid Tumor Specimen Repository. Patients with *KRAS* wt tumors were offered registration and randomization whereas patients with mutant *KRAS* tumors were ineligible. In July 2010, eligibility could be determined by testing for *KRAS* mutation in any Clinical Laboratory Improvement Amendments-certified laboratory, although specimen submission was mandated to confirm *KRAS* status by central review. Only patients with confirmed *KRAS* wt were included in this primary analysis. Following completion of the study, a subset of specimens were analyzed for expanded *RAS* status (see eMethods in Supplement 2 for *KRAS* and expanded *RAS* assays.)

Treatment

The choice of either the mFOLFOX6 or FOLFIRI chemotherapeutic regimen was made by the patient and physician prior to trial enrollment and randomization. From November 2005 to September 2009 patients were randomized 1:1:1 to receive cetuximab, bevacizumab, or both of these biologic treatments in combination with either the mFOLFOX6 or FOLFIRI regimen. Thereafter, patients were randomized 1:1 to cetuximab or bevacizumab biologic treatment. At randomization, the primary physician indicated whether the treatment goal was palliative or potentially curative. Randomization was stratified by (1) chemotherapeutic regimen administered (mFOLFOX6; FOLFIRI), (2) receipt of prior adjuvant chemotherapy, and (3) prior pelvic radiation. Patients were stratified for statistical analysis by the time of enrollment either before or after the *KRAS* amendment. Treatment assignments were generated according to randomly permuted blocks within strata. A fixed-block size of 9 was used prior to the study amendment that stopped enrollment into the double-biologic group. Afterward, a block size of 6 was used.

Cetuximab or bevacizumab was administered prior to cytotoxic chemotherapies: 400 mg/m^2 of cetuximab was infused intravenously over 120 minutes on day 1, then 250 mg/m^2 over 60 minutes every week, and 5 mg/kg of bevacizumab was infused over 90 minutes in week one. Assuming no adverse reactions, subsequent infusions were administered over 30 to 60 minutes every other week.

The FOLFIRI regimen was administered as 180 mg/m^2 of irinotecan over 90 minutes and 400 mg/m^2 of leucovorin over 2 hours followed by a 400-mg/m^2 bolus of fluorouracil, then a 2400-mg/m^2 bolus of fluorouracil by a 46- to 48-hour infusion repeated every 2 weeks. The mFOLFOX6 regimen was administered as 85 mg/m^2 of oxaliplatin over 120 minutes and 400 mg/m^2 of leucovorin over 2 hours followed by a 400-mg/m^2 bolus of fluorouracil then a 2400-mg/m^2 bolus of fluorouracil by a 46- to 48-hour infusion repeated every 2 weeks.

Patients received routine supportive care at the discretion of the treating physician. Standard-dose adjustment criteria were applied to both mFOLFOX6 and FOLFIRI regimens. Treatment for the acneiform skin reaction was at the discretion of the treating physician. Patients experiencing oxaliplatin or other infusion reactions were not rechallenged with treatment. Adverse events were assessed using the NCI Common Toxicity Criteria version 3.0.

Clinical Outcomes

The primary end point of overall survival was defined as time of study entry until death. Patients without reported deaths were censored at their last known follow-up. Secondary end points included response rate (site-reported confirmed or unconfirmed complete or partial response by RECIST [Response Evaluation Criteria in Solid Tumors]) and progression-free survival measured from study entry until first documented progression or death. For the progression-free survival end point, patients alive without documented tumor progression were censored for progression at the most recent disease assessment. An additional secondary end point was 60-day mortality assessed as the proportion of patients dying due to any cause within 60 days of beginning protocol therapy. The incidence of arterial thrombotic events in each treatment group was monitored throughout the trial. Patients were evaluated every 8 weeks for response by conventional cross-sectional imaging using the RECIST v1.0 criteria.[14] Patients maintained their study treatment until disease progression, unacceptable toxic effects, a gap of more than 28 days between treatments, or decision to discontinue treatment. Disease assessment was done by the treating investigator and was not blinded.

Statistical Methods

The primary statistical analyses were 2-sided tests of superiority comparing cetuximab vs bevacizumab with regard to the primary and main secondary outcomes among patients whose tumors were determined to be *KRAS* wt (exon 2, codons 12,13) by Southwest Oncology Group review using intention-to-treat analyses. Sample-size calculations considered a median overall survival of 22.0 months with bevacizumab based on Hurwitz et al[9] and a clinically meaningful difference of 5 to 6 months in median overall survival. The trial was designed to target a hazard ratio (HR) of 0.80

(an improvement from 22 to 27.5 months) with 90% power (2-sided α = .05). Based on these factors, 1142 patients and 849 primary outcome events were needed.

Interim analyses were conducted every 6 months after 15% of the expected number of overall survival outcome events were observed. The 2-sided Lan-DeMets analogue of O'Brien-Fleming boundaries was used to test the null hypothesis at each interim analysis according to the stratified log-rank test. Boundaries were truncated at 2.58; based on the actual boundaries used in the analyses, the 2-sided adjusted significance level at the final analysis was .06. A progression-free survival HR of 0.76 was detectable with 85% power based on a log-rank test (526 events; 2-sided α = .05). The Kaplan-Meier method was used to estimate overall and progression-free survival. The stratified log-rank test was used to compare overall survival between the biologics. No adjustments were made for multiple comparisons in the analysis of secondary end points. Thus, these analyses should be considered exploratory. Proportional hazards modeling was used to estimate HRs and associated 95% confidence intervals and to test interactions of sex, race (white vs nonwhite), and chemotherapy by treatment. Because white patients comprised 82% of the study sample, levels of race were collapsed to white vs nonwhite race for data analysis. Ethnicity was not considered other than descriptively. Hazard ratio estimates were adjusted for prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, and randomization before and after the study was amended. Due to the large number of enrollment sites, this variable was not considered in the analysis. Subset analyses were conducted in the expanded *RAS*, mFOLFOX6, and FOLFIRI subgroups. In addition, κ statistics were used to estimate agreement between institutional and central review of *KRAS* status.

Power was approximately 0.92 to detect a difference of 0.1 in the magnitude of response between treatment groups at the final analysis (2-sided α = .05). Within each treatment group, the hypothesis that the arterial thrombotic event rate was 0.5 or less was tested against the alternative, 0.08 or higher; 90% power was achieved to test this hypothesis (n = 571; 1-sided α = .05). The lower 90% confidence bound estimate for the κ statistic was used to estimate assay agreement with 0.75 as a benchmark. Analyses are based on clinical data and patient follow-up as of December 15, 2015. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SAS v9.2, SAS Institute Inc; R 3.1.1, http://www.r-project.org). Data quality was reviewed and audited by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

Results

From September 2005 to March 2012, 3058 patients were preregistered or registered, and 2334 patients were randomized to 1 of 3 treatment groups at 396 study sites. Of these, 1137 patients with confirmed *KRAS* wt tumors received bevacizumab (n = 559) or cetuximab (n = 578). The 804 patients randomized after and the 333 patients registered before the *KRAS* amendment was implemented comprise the final primary analysis cohort (**Figure 1**). Data were released by the Alliance Data and Safety Monitoring Board in January 2014 after the 11th interim analysis concluded with high probability that neither treatment group could meet the preplanned goal of a 5.5-month superior overall survival compared with the other. Results are reported for (1) the primary 2-group comparison between cetuximab and bevacizumab; (2) the comparison of cetuximab vs bevacizumab in an expanded *RAS* subset described above; and (3) the chemotherapy subgroups.

Patient and tumor characteristics are presented in **Table 1**. The treatment groups were well-balanced for age, sex, race, performance status, and site of primary tumor. Cure was the intent for 17.1% (99 of 578) of patients in the cetuximab group vs 13.2% (74 of 559) in the bevacizumab group. Ninety-six percent (1096 of 1137) of randomized patients with confirmed *KRAS* wt tumors started protocol therapy; 15 patients (1.1%) reported that they "withdrew prior to beginning protocol therapy" for an off-treatment reason: 7, bevacizumab; 8 ,cetuximab (Figure 1). See treatment administration and dose modification summary for details (eTable 2 in Supplement 2).

Patient Outcome

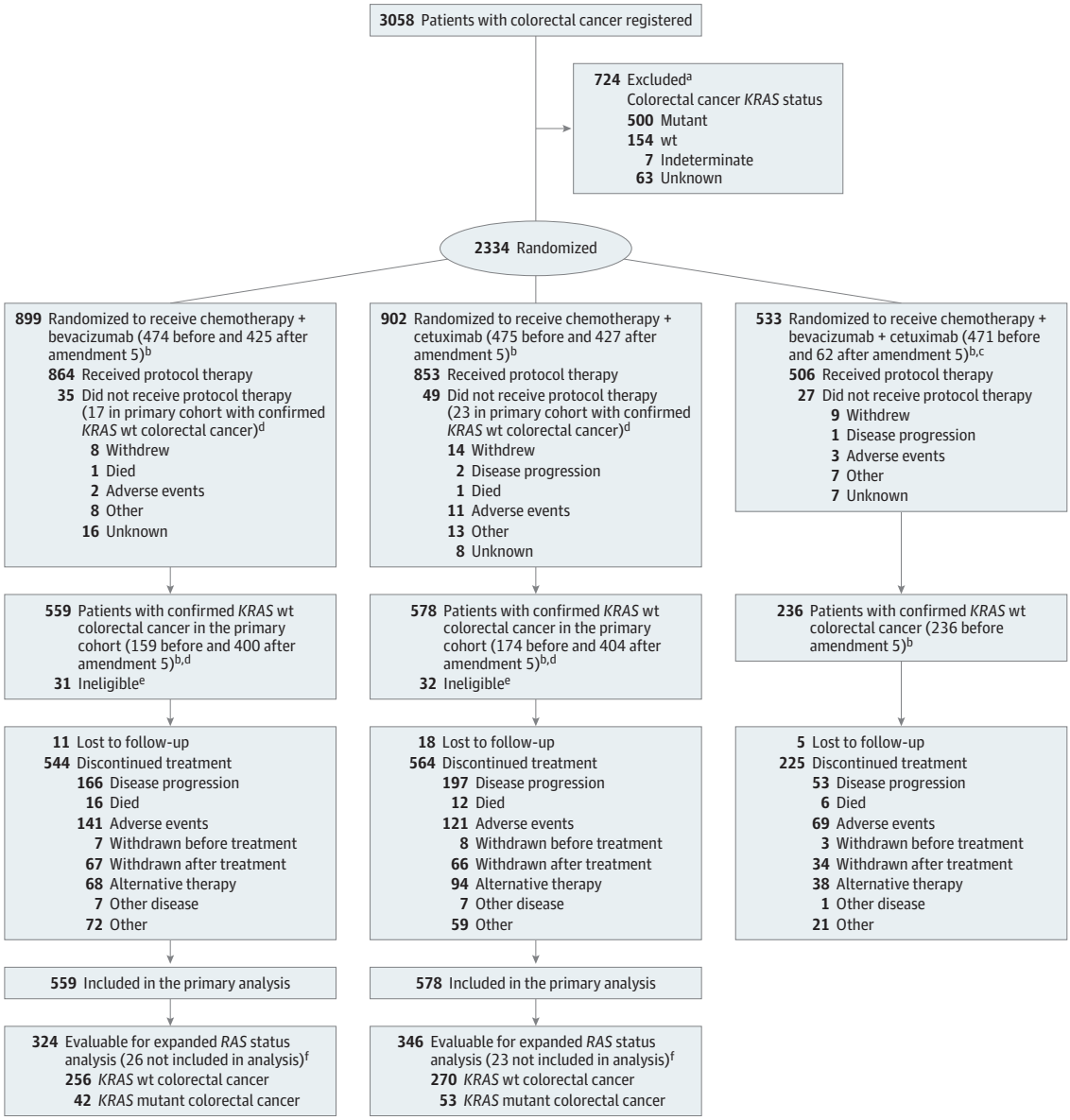
All randomized patients with confirmed *KRAS* wt tumors were evaluated. Among 235 patients enrolled with *KRAS* wt status by local assessment, 228 were confirmed by the Southwest Oncology Group (0.97; 95% CI, 0.94-0.99); the κ estimate for 239 patients with complete data was 0.52 with a 90% lower confidence bound estimate of 0.32. Of 1137 patients, 874 (76.9%) patients died. Median follow-up for surviving patients (n = 263) was 47.4 months (range, 0.0-110.7 months). Eighty-two percent of patients (938 of 1137) experienced disease progression. No significant differences were observed for either overall survival or progression-free survival in the primary analysis cohort. Median overall survival was 30.0 months in the cetuximab-chemotherapy group and 29.0 months in the bevacizumab-chemotherapy group (stratified HR, 0.88; 95% CI, 0.77-1.01; *P* = .08). Median progression-free survival was 10.5 months in the chemotherapy-cetuximab group and 10.6 months in the chemotherapy-bevacizumab (stratified HR, 0.95; 95% CI, 0.84-1.08; *P* = .45; **Figure 2** and eFigure 3 in Supplement 1). Response rates were 55.2% (309 of 559) in the bevacizumab group and 59.6% (345 of 578) in the cetuximab group (difference, 4.4%; 95% CI, 1.0%-9.0%; χ^2 *P* = .13).

The combination of chemotherapy and surgery rendered 140 patients disease free; median overall survival for the bevacizumab group was 62.2 months (95% CI, 49.4 months to not reached) and 64.7 months for the cetuximab group (95% CI, 51.6 months to not reached). Fifty-eight patients remained alive and disease free on the last data survey.

Post Hoc Analyses

Unplanned subgroup analyses were conducted for the expanded *RAS*, sex, race, and chemotherapy subsets. The results for overall survival (HR, 0.88; 95% CI, 0.72-1.08) and progression-free survival (HR, 1.03; 95% CI, 0.86-1.24) in the

Figure 1. Flow of Patients Through Cancer and Leukemia B Group and Southwest Oncology Group 80405 Trial



[a] The reasons patients with wild-type (wt), indeterminate, or unknown *KRAS* status were excluded were not captured at the time of exclusion.

[b] Amendment 5 limited trial eligibility to only patients with *KRAS* wild-type colorectal cancer in November 2008.

[c] This double-biologic treatment group was dropped from the trial and primary analysis based on amendment 6, which was established September 2009.

[d] The primary cohort comprises patients whose *KRAS* wt colorectal cancer was centrally confirmed by the Southwest Oncology Group and who had consented for the use of their specimens.

[e] Reasons for ineligibility in the primary cohort were not captured.

[f] Forty-nine tumor samples lacked sufficient DNA or analyses were incomplete.

expanded *RAS* wt cohort were similar to those in the full cohort (Figure 2 and eFigure 3 in Supplement 2). Baseline characteristics were comparable between patients with and without expanded *RAS* results. No significant interactions were observed for sex (HR for interaction, 0.92; 95% CI, 0.70-1.21) or race (HR for interaction, 1.04; 95% CI, 0.71-1.51) by biologic. A difference in overall survival was observed with mFOLFOX6 in favor of cetuximab (HR, 0.83; 95% CI, 0.71-0.98; eFigure 4 in Supplement 2) but not with FOLFIRI, for which the HR for overall survival was 1.04 (CI 95%, 0.79-1.35). The chemotherapy by biologic interaction HR for overall survival was 1.27 (95% CI, 0.94-1.73; *P* for interaction, .11; eFigures 4 and 5 in Supplement 2).

Adverse Events

Among 1137 patients, 1092 patients (96%) reported at least 1 adverse event: 584 patients (53%) experienced grade 3 or higher and 153 (14%) experienced grade 4 or higher adverse events.

Table 1. Patient and Tumor Characteristics by Treatment for Patients With *KRAS* Wild-Type (codons 12, 13) Metastatic Colorectal Cancer

Characteristic	No. (%) of Patients		
	Chemotherapy + Bevacizumab (n = 559)	Chemotherapy + Cetuximab (n = 578)	Total (N = 1137)
Age, median (range), y	59.0 (21.8-85.0)	59.2 (20.8-89.5)	59.1 (20.8-89.5)
Men	348 (62.3)	349 (60.4)	697 (61.3)
Women	211 (37.7)	229 (39.6)	440 (38.7)
Race			
Unknown	13 (2.3)	16 (2.8)	29 (2.6)
White	465 (83.2)	469 (81.1)	934 (82.1)
Black	64 (11.4)	65 (11.2)	129 (11.3)
Asian	13 (2.3)	22 (3.8)	35 (3.1)
Native Hawaiian or Pacific Islander	0	3 (0.5)	3 (0.3)
American Indian or Alaska Native	3 (0.5)	3 (0.5)	6 (0.5)
Not reported	1 (0.2)	0 (0.0)	1 (0.1)
Ethnicity			
Hispanic or Latino	35 (6.3)	37 (6.4)	72 (6.3)
Non-Hispanic	495 (88.6)	519 (89.8)	1014 (89.2)
Not reported	2 (0.4)	1 (0.2)	3 (0.3)
Unknown	27 (4.8)	21 (3.6)	48 (4.2)
Eastern Cooperative Oncology Group Performance Status[a]			
0	324 (58.0)	333 (57.6)	657 (57.8)
1	233 (41.7)	245 (42.4)	478 (42.0)
2	2 (0.4)	0	2 (0.2)
Tumor biology			
Metachronous (metastasis subsequent to diagnosis of primary tumor)	112 (20.0)	124 (21.5)	236 (20.8)
Synchronous (metastases present at diagnosis of primary tumor)	445 (79.6)	447 (77.3)	892 (78.5)
Unknown	2 (0.4)	7 (1.2)	9 (0.8)
Colorectal tumor location			
Left	334 (59.7)	355 (61.4)	689 (60.6)
Right	142 (25.4)	138 (23.9)	280 (24.6)
Transverse	31 (5.5)	31 (5.4)	62 (5.5)
Multiple	0	1 (0.2)	1 (0.1)
Unknown	52 (9.3)	53 (9.2)	105 (9.2)
Primary tumor unresected at study entry			
No	409 (73.1)	436 (75.4)	845 (74.3)
Yes	150 (26.8)	142 (24.5)	292 (25.7)
Protocol chemotherapy			
mFOLFOX6	409 (73.2)	426 (73.7)	835 (73.4)
FOLFIRI	150 (26.8)	152 (26.3)	302 (26.6)
Prior pelvic radiation			
No	509 (91.1)	526 (91.0)	1035 (91.0)
Yes	50 (8.9)	52 (9.0)	102 (9.0)
Prior adjuvant chemotherapy			
No	478 (85.5)	499 (86.3)	977 (85.9)
Yes	81 (14.5)	79 (13.7)	160 (14.1)
Disease description			
Missing	5 (0.9)	4(0.7)	9 (0.8)
Locally advanced	14 (2.5)	12 (2.1)	26 (2.3)
Metastatic	540 (96.6)	562 (97.2)	1102 (96.9)

(continued)

Table 1. Patient and Tumor Characteristics by Treatment for Patients With *KRAS* Wild-Type (codons 12, 13) Metastatic Colorectal Cancer (continued)

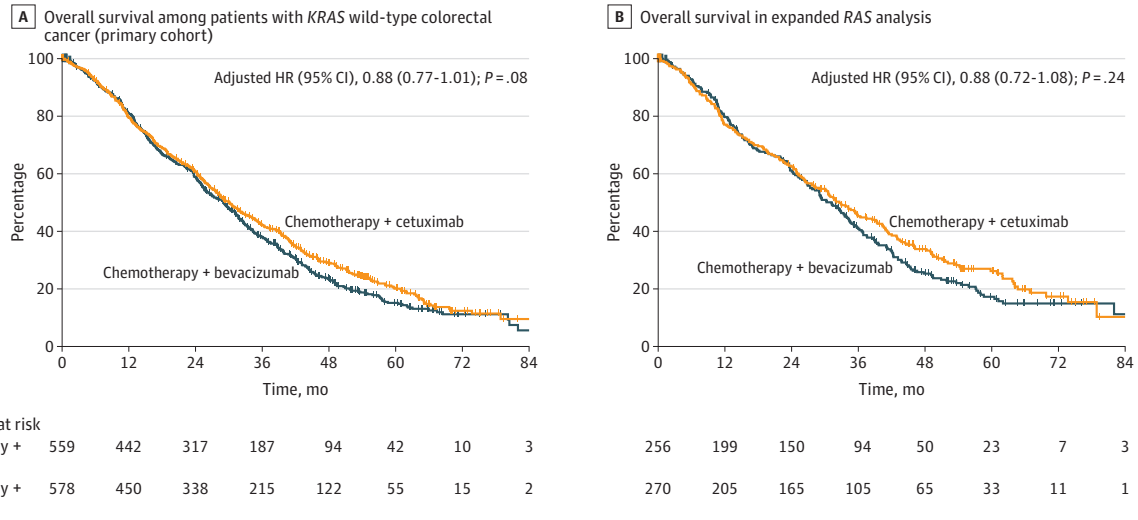
Characteristic	No. (%) of Patients		
	Chemotherapy + Bevacizumab (n = 559)	Chemotherapy + Cetuximab (n = 578)	Total (N = 1137)
Intent of treatment			
Missing	17 (3.0)	18 (3.0)	35 (3.1)
Palliative	468 (83.7)	461 (79.7)	929 (81.7)
Curative intent	74 (13.3)	99 (17.3)	173 (15.2)
Metastatic sites[b]			
Primary site or tumor bed	161 (29.1)	136 (23.7)	297 (26.3)
Intra-abdominal	127 (22.9)	134 (23.3)	261 (23.1)
Bone	16 (2.9)	17 (3.0)	33 (2.9)
Lung	182 (32.9)	185 (32.2)	367 (32.5)
Any liver	411 (74.2)	421 (73.3)	832 (73.8)
Liver only	165 (29.5)	187 (32.3)	352 (30.9)
Central nervous system including brain	0	1 (0.2)	1 (0.1)
Other	92 (16.6)	92 (16.0)	184 (16.3)

Abbreviations: FOLFIRI, leucovorin, fluorouracil, and irinotecan; mFOLFOX6, leucovorin, fluorouracil, and oxaliplatin.

[a] The 0-to-5 coded scale describing patient daily level of functioning from fully active (0) to completely disabled (4); dead (5). As published in Oken et al.[24]

[b] Sites are not mutually exclusive except for "Liver only."

Figure 2. Kaplan-Meier Estimates of Overall Survival Among Patients Randomized to Bevacizumab or Cetuximab



Tick marks on the curves denote the last known follow-up time for patients with no death date reported. The hazard ratio and *P* value are adjusted for prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, and randomization before and after the amendment restricting eligibility to the *KRAS* wild-type tumor. Hazard ratio and *P* value for the *RAS* analysis are adjusted for prior adjuvant therapy, prior radiotherapy, protocol chemotherapy, and randomization before or after the amendment restricting eligibility to *KRAS* wild type tumor (*KRAS* is defined as exon 2 codons 12, 13; exon 4, codons 117, 146; exon 3 codons 59, 61 or *NRAS*: exon 2 codons 12, 13; exon 3 codons 59, 61; exon 4 codons 117, 146).

Thirty-one patients died while receiving the protocol therapy: 16, bevacizumab; 15, cetuximab. The deaths of 8 patients in the bevacizumab group and 7 in the cetuximab group could possibly be related to the protocol treatment. Adverse events reported in at least 10% of patients were not different across groups (**Table 2**). Toxic effects that were lower than grade 3 were distinct with acneiform rash predominating for cetuximab and hypertension predominating for bevacizumab. The rate of arterial thrombotic events was not statistically higher than 5% on either regimen. No significant difference in 60-day mortality was observed (1.4% [8 of 555] for bevacizumab; 2.0% [12 of 571] for cetuximab (Fisher exact test, *P* = .50).

Discussion

In this clinical trial involving patients with advanced or metastatic *KRAS* wt colorectal cancer, there was no significant difference in overall survival with treatment using cetuximab vs bevacizumab added to the mFOLFOX6 or FOLFIRI chemotherapeutic regimens as first-line treatments. These findings persisted following exclusion of patients with any *RAS* mutations.

When planning this randomized clinical trial, a 22-months' median survival was expected for the combination of bevacizumab and the chemotherapeutic regimen, yet survival

was at least 29 months in both groups. Better chemotherapeutic regimens, patient selection, and changing multidisciplinary management likely contributed to these outcomes as did the exclusion of patients with *KRAS* mutations. This eligibility change increased the proportion of study patients who might benefit from cetuximab but also improved the prognosis for the entire group by eliminating patients with negatively prognostic *RAS* mutations. Also, patients in this study likely had lower tumor burden compared with patients who participated in earlier studies as a result of better imaging at diagnosis as well as the coincidental detection of small cancers when patients undergo diagnostic imaging for other indications. The majority of patients also had access to both cetuximab and bevacizumab at progression because each biologic therapy was commercially available. Patients who received any subsequent treatment could have changed chemotherapy and either crossed over to or continued with bevacizumab beyond tumor progression.[15] Twelve percent of patients were rendered temporarily disease free (41% remained without evidence of cancer at a median of 5.5 years' follow-up) with surgery of all sites of disease. This also contributed to the survival results. In addition, some patients may have benefitted from subsequent experimental or off-label treatments,

These results differ from 2 smaller but contemporary studies that asked a similar question. First, the FIRE-3 trial (n=592) led by the Arbeitsgemeinschaft Internistische Onkologie cooperative group (AIO)[16] also compared cetuximab and bevacizumab but differed from the present study in that the chemotherapy was limited to FOLFIRI and the primary outcome was investigator-adjudicated response rate. This trial found no significant difference in response rate (62% vs 58%, P = .18) between cetuximab and bevacizumab biologic therapies. However, overall survival favored cetuximab by 3.7 months (28.7 vs 25.0 months) and was even more favorable with expanded *RAS* analysis (33.1 vs 25.6 months; P = .011). Second, the PEAK (Panitumumab Efficacy in Combination With mFOLFOX6 Against Bevacizumab Plus mFOLOFOX6 in mCRC Subjects With Wild-Type KRAS Tumors) trial[17] enrolled 285 patients but compared panitumumab (a fully humanized anti-EGFR antibody) to bevacizumab in combination with FOLFOX. The primary outcome of progression-free survival was not statistically different between the panitumumab and bevacizumab treatment groups (10.9 vs 10.1 months, P = .35). However, there was a significant difference in overall survival between panitumumab and bevacizumab (34.2 vs 24.3 months; P = .009).

Neither of these studies mandated subsequent treatment choices (although FIRE-3 had recommended specific second-line treatments per protocol). Furthermore, the variances in management preferences across the world can have important effects on overall survival. The FIRE-3 investigators made an effort to document subsequent treatments and postulated that patients receiving first-line cetuximab treatment would have better overall survival because of a biological advantage when an EGFR inhibitor is followed by bevacizumab.[18] However, a poorer overall survival for patients receiving bevacizumab in FIRE-3 compared with this study accounts for most of the survival difference (expanded *RAS*, chemotherapy + bevacizumab, overall survival for 80405 was 31.2 months; for FIRE-3,25.6 months). The use of bevacizumab beyond progression after FOLFIRI and bevacizumab[18] in patients in the FIRE-3 study (11% of the 68% of patients who received any second-line treatment) is infrequent compared with its routine use in the United States. This is speculative, however, because the collection of subsequent treatment details across hundreds of sites in North America is extremely difficult and the details of such data would be open to questioning no matter the resources put into such an effort. Therefore, the sequencing theory promulgated by FIRE-3 investigators is not addressed.

This study has several limitations. First, the imbalance in choice of mFOLFOX6 vs FOLFIRI regimens limits the ability to statistically compare the cytotoxic chemotherapy regimens and any possible interaction with the antibodies. Second, this study only mandated first-line treatment with patients who at any time went more than 28 days without treatment being removed from study. Because treatment holidays were used more commonly during the course of the study and because collection of the details of treatment

Table 2. Grade 3 or More Adverse Events at Least Possibly Related to Treatment and Occurring in at Least 10% of Patients in Either Treatment Group (Maximum Grade per Patient per Event)

	No. (%)	
	Chemotherapy + Bevacizumab (n = 539)	Chemotherapy + Cetuximab (n = 553)
Hematologic Adverse Events		
Blood or bone marrow, grade[a]		
3	125 (23)	137 (25)
4	35 (6)	37 (7)
5	0	0
Nonhematologic Adverse Events		
Fatigue (asthenia, lethargy, malaise), grade[b]		
3	39 (7)	49 (9)
4	4 (1)	3 (1)
5	0	0
Diarrhea, grade[b]		
3	45 (8)	60 (11)
4	1 (<1)	0
5	0	0
Sensory neuropathy, grade[b]		
3	72 (13)	73 (13)
4	3 (1)	0
5	0	0

[a] Grade 3 indicates absolute neutrophils count of less than 1000/μL to 500/μL or absolute granulocytes count of less than 1.0 × 10^9/L to 0.5 × 10^9/L; grade level 4, absolute neutrophils count of less than 500/μL or absolute granulocytes count of less than 0.5 × 10^9/L; and grade level 5, death.

[b] Grade 3 indicates severe; grade 4, life threatening; and grade 5, death.

drugs and schedules, dosing and complications has been challenging, it is difficult to infer the effects of subsequent management decisions. Third, one element not included in the on-study information was primary cancer site (eg, right vs left colon). This information was collected post hoc through chart review and has been suggested to influence outcome as a biologic surrogate.[19]

Conclusions

Among patients with *KRAS* wt untreated advanced or metastatic colorectal cancer, there was no significant difference in overall survival between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment.

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REFERENCES

1. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol*. 1992;10(6):896-903.

2. O'Dwyer PJ, Paul AR, Walczak J, Weiner LM, Litwin S, Comis RL. Phase II study of biochemical modulation of fluorouracil by low-dose PALA in patients with colorectal cancer. *J Clin Oncol*. 1990;8(9):1497-1503.

3. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000;355(9209):1041-1047.

4. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947.

5. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22(2):229-237.

6. Grothey A, Sargent D, Goldberg RM, Schmoll H-J. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004;22(7):1209-1214.

7. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-345.

8. Chung KY, Shia J, Kemeny NE, et al. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol*. 2005;23(9):1803-1810.

9. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342.

10. Saltz LB, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26 (12):2013-2019.

11. Lièvre A, Bachet J-B, Boige V, et al. *KRAS* mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol*. 2008;26(3):374-379.

12. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med*. 2009;360(6): 563-572.

13. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol*. 2009;27 (5):672-680.

14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92:205-216.

15. Bennouna J, Sastre J, Arnold D, et al; ML18147 Study Investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(1):29-37.

16. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1065-1075.

17. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type *KRAS* exon 2 metastatic colorectal cancer. *J Clin Oncol*. 2014;32(21):2240-2247.

18. Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of subsequent therapies on outcome of the FIRE-3/AIO KRK0306 trial: first-line therapy with FOLFIRI plus cetuximab or bevacizumab in patients with KRAS wild-type tumors in metastatic colorectal cancer. *J Clin Oncol*. 2015;33(32):3718-3726.

19. Venook AP, Niedzwiecki D, Innocenti F, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). http://meetinglibrary.asco.org/record/123617/abstract. Presented June 25, 2016. Accessed May 26, 2017.

20. Shi Q, de Gramont A, Grothey A, et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. *J Clin Oncol*. 2015;33(1):22-28.

21. Heinemann V, Niedzwiecki D, Pearline R, et al. Outcomes for FOLFIRI plus bevacizumab (BEV) or cetuximab (CET) in patients previously treated with oxaliplatin-based adjuvant therapy: a combined analysis of data from FIRE-3 and CALGB 80405. http://meetinglibrary.asco.org/record/112003/video. Presented June 1, 2015. Accessed May 26, 2017.

22. O'Neil BH, Venook AP. Trying to understand differing results of FIRE-3 and 80405: does the first treatment matter more than others? *J Clin Oncol*. 2015;33(32):3686-3688.

23. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21(11):1350-1356.

24. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649-655.