ORIGINAL ARTICLE

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

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ABSTRACT

BACKGROUND

We investigated the efficacy of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) as first-line treatment for metastatic colorectal cancer and sought associations between the mutation status of the *KRAS* gene in tumors and clinical response to cetuximab.

METHODS

We randomly assigned patients with epidermal growth factor receptor–positive colorectal cancer with unresectable metastases to receive FOLFIRI either alone or in combination with cetuximab. The primary end point was progression-free survival.

RESULTS

A total of 599 patients received cetuximab plus FOLFIRI, and 599 received FOLFIRI alone. The hazard ratio for progression-free survival in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% confidence interval [CI], 0.72 to 0.99; P=0.048). There was no significant difference in the overall survival between the two treatment groups (hazard ratio, 0.93; 95% CI, 0.81 to 1.07; P=0.31). There was a significant interaction between treatment group and *KRAS* mutation status for tumor response (P=0.03) but not for progression-free survival (P=0.07) or overall survival (P=0.44). The hazard ratio for progression-free survival among patients with wild-type–*KRAS* tumors was 0.68 (95% CI, 0.50 to 0.94), in favor of the cetuximab–FOLFIRI group. The following grade 3 or 4 adverse events were more frequent with cetuximab plus FOLFIRI than with FOLFIRI alone: skin reactions (which were grade 3 only) (in 19.7% vs. 0.2% of patients, P<0.001), infusion-related reactions (in 2.5% vs. 0%, P<0.001), and diarrhea (in 15.7% vs. 10.5%, P=0.008).

CONCLUSIONS

First-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The benefit of cetuximab was limited to patients with *KRAS* wild-type tumors. (ClinicalTrials.gov number, NCT00154102.)

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Colorectal cancer is the third most common cancer worldwide.[1] Approximately 25% of patients with colorectal cancer present with overt metastatic disease, and metastatic disease develops in 40 to 50% of newly diagnosed patients. Standard first-line treatments include fluorouracil with leucovorin and irinotecan[2,3] or oxaliplatin,[4] alone or combined with bevacizumab.[5]

The immunoglobulin G1 monoclonal antibody against the epidermal growth factor receptor (EGFR), cetuximab (Erbitux), is effective in combination with irinotecan in patients with metastatic colorectal cancer or as a single agent in patients with metastatic colorectal cancer that progresses even when irinotecan is used.[6,7] Phase 1 and 2 studies have shown cetuximab to have activity when added to irinotecan-based therapy[8,9] or oxaliplatin-based therapy[10-12] as first-line treatment.

There are no biomarkers that reliably predict responses to cetuximab, but the examination of outcomes based on the presence of mutations of the *KRAS* gene shows promise. *KRAS* encodes a small G protein that links ligand-dependent receptor activation to intracellular pathways of the EGFR signaling cascade. Mutation at key sites within the gene, commonly at codons 12 and 13, causes constitutive activation of KRAS-associated signaling. Growing evidence indicates that tumor *KRAS* mutation is associated with the inefficacy of cetuximab[13-17] and the monoclonal anti-EGFR immunoglobulin G2 antibody panitumumab.[18,19]

In our multicenter phase 3 trial, Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL), we investigated the efficacy and safety of irinotecan in combination with a simplified regimen of fluorouracil and leucovorin (FOLFIRI) plus cetuximab[20] in the initial treatment of metastatic colorectal cancer. We also conducted a retrospective subgroup analysis to investigate the influence of the tumor *KRAS* mutation status on outcome.

METHODS

PATIENTS

Inclusion criteria were an age of 18 years or older, histologically confirmed adenocarcinoma of the colon or rectum, first occurrence of metastatic disease that could not be resected for curative purposes, immunohistochemical evidence of tumor EGFR expression, Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less, and adequate hematologic, hepatic, and renal function. Exclusion criteria were previous exposure to an anti-EGFR therapy or irinotecan-based chemotherapy, previous chemotherapy for metastatic colorectal cancer, adjuvant treatment that was terminated 6 months or less before the start of treatment in our trial, and the use of radiotherapy, surgery (excluding previous diagnostic biopsy), or any investigational drug in the 30-day period before the start of treatment in our trial.

The protocol was approved by independent ethics committees and the governmental authorities in each country, as required. The trial was carried out in accordance with the Declaration of Helsinki (October 1996). All patients provided written and oral informed consent.

STUDY DESIGN

This trial was a randomized, open-label, multicenter study comparing 14-day cycles of cetuximab plus FOLFIRI and FOLFIRI alone. We randomly assigned patients (in a 1:1 ratio) to one of the two treatment groups using a stratified permuted-block procedure, with ECOG performance status (0 or 1 vs. 2) and region (sites in Western Europe vs. Eastern Europe vs. outside Europe) as stratification factors.

The primary end point was progression-free survival time, defined as the time from randomization to disease progression or death from any cause within 60 days after the last tumor assessment or after randomization. Secondary end points included the overall survival time, the rate of best overall response (the proportion of patients with a confirmed complete response or partial response, defined as a response persisting for at least 28 days), and safety end points (including the incidence and type of adverse events, laboratory variables, and vital signs).

The number of patients undergoing surgery with a curative intent (any resection of metastasis with a goal of cure or complete resection of all lesions to R0) was prospectively analyzed. A retrospective subgroup analysis was used to investigate associations between the progression-free survival time, overall survival time, or response rate and the *KRAS* mutation status of tumors. An independent review committee (consisting of radiologists and oncologists) performed a preplanned, blinded, retrospective review (based on modified

World Health Organization criteria) of radiologic assessments and clinical data to determine the day of progression and the best overall response.

The study was designed by Merck (Darmstadt) together with the primary academic investigator. Data were collected by principal investigators at each center, and statistical analyses were conducted by a contract research organization (Quintiles), supervised by Merck (Darmstadt). The primary academic investigator had access to all the data and vouches for the completeness and accuracy of the reported data and the analyses.

TREATMENT

On day 1 of each 14-day period during the study, patients in the FOLFIRI group received a 30- to 90-minute infusion of irinotecan at a dose of 180 mg per square meter of body-surface area; an infusion, for 120 minutes, of racemic leucovorin or L-leucovorin at a dose of 400 or 200 mg, respectively, per square meter of body-surface area; fluorouracil in a bolus of 400 mg per square meter of body-surface area and then continuous infusion for 46 hours of 2400 mg per square meter of body-surface area.

During the study, patients in the cetuximab–FOLFIRI group received cetuximab in an initial 120-minute infusion on day 1 of 400 mg per square meter of body-surface area, followed by 60-minute infusions of cetuximab at a dose of 250 mg per square meter of body-surface area, once weekly (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). FOLFIRI was given after the cetuximab infusion on day 1 of each period.

Treatment was continued until disease progression, unacceptable toxic effects, or withdrawal of consent occurred. In the event of predefined toxic effects related to chemotherapy or cetuximab, protocol-specified treatment modifications were permitted.

ASSESSMENTS

Computed tomography or magnetic resonance imaging was performed every 8 weeks until disease progression was observed to have occurred. Follow-up evaluations were performed every 3 months. Adverse events (the severity of which were assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0) and concomitant medication use were recorded continuously.

KRAS MUTATION STATUS

DNA was extracted from formaldehyde-fixed, paraffin-embedded tumor-biopsy specimens and screened for *KRAS* mutations in codons 12 and 13 with the use of a polymerase-chain-reaction (PCR) clamping and melting curve method[21] (implemented by means of a LightMix k-ras Gly12 assay, TIB MOLBIOL). PCR amplification of the wild-type *KRAS* sequence was suppressed in this process by the incorporation in the reaction mix of a locked nucleic-acid oligomer[22] spanning codons 12 and 13 of the *KRAS* gene (see the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

We aimed to enroll enough patients to yield the occurrence of 633 progression events, which would give a statistical power of 80% to reject the null hypothesis of no significant difference in the progression-free survival time between the two treatment groups, assuming a hazard ratio of 0.8 and a significance level of a two-sided log-rank test fixed at 5%. All statistical-analysis methods were prespecified. All reported P values are two-sided and were not adjusted for multiple testing.

Analysis of the progression-free survival time was based on Kaplan–Meier curves (product-limit estimates)[23] and performed on all patients who received at least one dose of a study drug. Results between the two treatment groups were compared with the use of a log-rank test[24] after stratification according to the ECOG performance status and region. Secondary efficacy analyses were supportive, exploratory, and nonconfirmatory. The rates of best overall response and surgery with curative intent were compared between the two treatment groups with the use of a Cochran–Mantel–Haenszel test,[25] stratified according to the randomization strata. The efficacy-analysis methods were repeated for the subgroup with samples that could be evaluated for *KRAS* mutation status (the *KRAS* population). The heterogeneity of treatment effects between the subgroups with wild-type and mutant *KRAS* was explored retrospectively with the use of a statistical test for interaction applied through a Cox model for progression-free survival time and overall survival time and a logistic-regression model for overall response rate. Hazard and odds ratios are expressed for cetuximab plus FOLFIRI as compared with FOLFIRI alone.

Safety analyses were carried out with the use of data from all patients receiving at least one dose of any study drug. Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (version 10.0) system organ classes and preferred terms, as well as predefined special adverse event categories in which the preferred terms are pooled.

RESULTS

PATIENTS

From July 2004 through November 2005, 2020 patients were screened at 189 of the 201 centers, and 1217 underwent randomization, of which 1198 were subsequently treated (599 in each of the two groups) at 184 centers (Fig. 2 in the Supplementary Appendix). Four patients were treated but did not undergo randomization; therefore, the safety population comprised 1202 patients (600 receiving cetuximab plus FOLFIRI and 602 receiving FOLFIRI alone).

In the safety population, the cetuximab–FOLFIRI group had a median duration of 25.0 weeks (interquartile range, 12.9 to 40.4) of cetuximab treatment, 26.0 weeks (interquartile range, 14.0 to 40.3) of irinotecan treatment, and 26.0 weeks (interquartile range, 13.8 to 40.4) of fluorouracil treatment. The FOLFIRI group had a median duration of 25.7 weeks (interquartile range, 15.1 to 35.9) of irinotecan treatment and 25.7 weeks (interquartile range, 14.9 to 36.0) of fluorouracil treatment. The median duration of follow-up was 29.9 months (95% confidence interval [CI], 29.1 to 30.5) with cetuximab plus FOLFIRI and 29.4 months (95% CI, 28.8 to 30.4) with FOLFIRI alone. Seven patients were lost to follow-up — two in the cetuximab–FOLFIRI group and five in the FOLFIRI group. In the primary analysis population, post-study chemotherapy with or without EGFR antibody therapy was administered to 63.9% and 6.2% of patients, respectively, receiving cetuximab plus FOLFIRI and 68.8% and 25.4%, respectively, of those receiving FOLFIRI. The findings were similar for the *KRAS* population.

The study groups were well balanced in terms of baseline characteristics with regard to the patients, disease, and treatment (Table 1). Altogether, 60.5% of the study population was male, 96.5% had an ECOG performance status of 0 or 1, and the colon was the primary tumor site in 60.2%.

EFFICACY

Progression events occurred in 298 patients receiving cetuximab plus FOLFIRI and 322 receiving FOLFIRI alone; cetuximab–FOLFIRI treatment reduced the risk of progression by 15% as compared with FOLFIRI alone (adjusted hazard ratio for cetuximab–FOLFIRI, 0.85; 95% CI, 0.72 to 0.99; P=0.048) (Fig. 1A and Table 2). The median progression-free survival times were 8.9 months with cetuximab plus FOLFIRI and 8.0 months with FOLFIRI alone. As of the cutoff date for collection of survival data of December 31, 2007, there were 412 deaths in the cetuximab–FOLFIRI group and 416 in the FOLFIRI group. The adjusted hazard ratio for death with cetuximab plus FOLFIRI was 0.93 (95% CI, 0.81 to 1.07; P=0.31) (Fig. 1B). Median overall survival times were 19.9 months in the cetuximab–FOLFIRI group and 18.6 months in the FOLFIRI group (Table 2). Confirmed complete or partial tumor responses occurred in 281 patients (46.9%) receiving cetuximab plus FOLFIRI and in 232 patients (38.7%) receiving FOLFIRI alone. The adjusted odds ratio for a tumor response with cetuximab–FOLFIRI treatment, as compared with FOLFIRI alone, was 1.40 (95% CI, 1.12 to 1.77; P=0.004) (Table 2). The rate of surgery for metastases was higher in the cetuximab–FOLFIRI group than in the FOLFIRI group (7.0% vs. 3.7%), as was the rate of R0 resection with curative intent before disease progression (4.8% vs. 1.7%; odds ratio for cetuximab–FOLFIRI, 3.02; 95% CI, 1.45 to 6.27; P=0.002).

SUBGROUP ANALYSIS ACCORDING TO *KRAS* MUTATION STATUS

Tumor samples obtained at baseline from 540 patients were suitable for the analysis of *KRAS* mutation status; samples from the remaining patients were either of insufficient size or not available. Tumors of 348 patients (64.4%) had wild-type *KRAS* and those of 192 patients (35.6%) had mutated *KRAS*. More patients in the FOLFIRI group than in the cetuximab–FOLFIRI group had wild-type–*KRAS* tumors (66.9% vs. 62.1%). The hazard ratios for progression were similar in the primary analysis population (0.85) and the *KRAS* population (0.82).

The association between *KRAS* mutation status and treatment, with regard to progression-free survival, was not significant (P=0.07), nor was there a significant treatment interaction for over-

Table 1. Baseline Characteristics of the Study Patients in the Primary Analysis Population and the *KRAS* Population, According to Treatment Group.*

Variable	Primary Analysis Population		*KRAS* Population		Wild-Type *KRAS*		Mutant *KRAS*	
	Cetuximab plus FOLFIRI (N=599)	FOLFIRI Alone (N=599)	Cetuximab plus FOLFIRI (N=277)	FOLFIRI Alone (N=263)	Cetuximab plus FOLFIRI (N=172)	FOLFIRI Alone (N=176)	Cetuximab plus FOLFIRI (N=105)	FOLFIRI Alone (N=87)
Male sex (%)	61.6	59.4	62.1	53.2	61.0	54.5	63.8	50.6
Age (yr)								
Median	61	61	61	62	61	60.5	62	63
Range	22–82	19–84	22–79	22–79	24–79	22–79	22–79	32–79
Region (%)								
Eastern Europe	33.9	33.6	50.2	51.7	48.8	48.9	52.4	57.5
Western Europe	43.7	44.6	41.9	43.3	41.3	46.0	42.9	37.9
Outside Europe	22.4	21.9	7.9	4.9	9.9	5.1	4.8	4.6
ECOG performance status (%)†								
0	55.1	53.1	55.2	54.8	57.6	59.1	51.4	46.0
1	41.1	43.4	40.8	42.6	38.4	36.9	44.8	54.0
2	3.5	3.5	4.0	2.7	4.1	4.0	3.8	0.0
Laboratory values (%)								
Lactate dehydrogenase >ULN	44.6	44.7	46.9	44.5	46.5	41.5	47.6	50.6
Alkaline phosphatase ≥300 U/liter	11.9	13.3	10.1	9.9	8.1	9.7	13.3	10.3
Leukocyte count >10,000/mm^3	19.9	15.7	16.6	20.2	16.3	16.5	17.1	27.6
Previous therapy (%)								
Adjuvant chemotherapy	18.9	17.4	16.2	14.8	19.2	16.5	11.4	11.5
Radiotherapy pretreatment	10.5	11.7	12.6	12.9	16.9	13.6	5.7	11.5
Site of primary tumor (%)								
Colon	59.8	60.4	58.1	59.3	55.2	58.5	62.9	60.9
Rectum	38.1	37.6	40.4	39.9	44.2	40.9	34.3	37.9
Colon or rectum	2.0	1.8	1.1	0.8	0.6	0.6	1.9	1.1
Missing data	0.2	0.2	0.4	0.0	0.0	0.0	1.0	0.0
Metastases (%)								
At one or two sites	83.5	86.1	84.8	84.4	86.0	84.7	82.9	83.9
Confined to liver	20.4	22.4	18.8	21.3	19.8	18.2	17.1	27.6

* FOLFIRI denotes fluorouracil, irinotecan, and leucovorin, and ULN the upper limit of the normal range.
† The Eastern Cooperative Oncology Group (ECOG) performance status score can range from 0 to 2, with higher scores indicating greater impairment.

all survival (P=0.44). There was, however, a significant interaction of mutation status with tumor response (P=0.03).

Hazard ratios for progression-free survival among patients receiving cetuximab plus FOLFIRI, as compared with FOLFIRI alone, who had tumors with wild-type *KRAS* and who had tumors with mutant *KRAS* were 0.68 (P=0.02) and 1.07 (P=0.75), respectively (Fig. 1C and 2A). Median progression-free survival times with cetuximab–FOLFIRI and FOLFIRI were 9.9 months and 8.7 months, respectively, in the wild-type–*KRAS* population and 7.6 and 8.1 months, respectively, in the mutant-*KRAS* population. Hazard ratios for overall survival in the wild-type–*KRAS* and mutant-*KRAS* populations were 0.84 and 1.03, respectively (Fig. 1D and 2A).

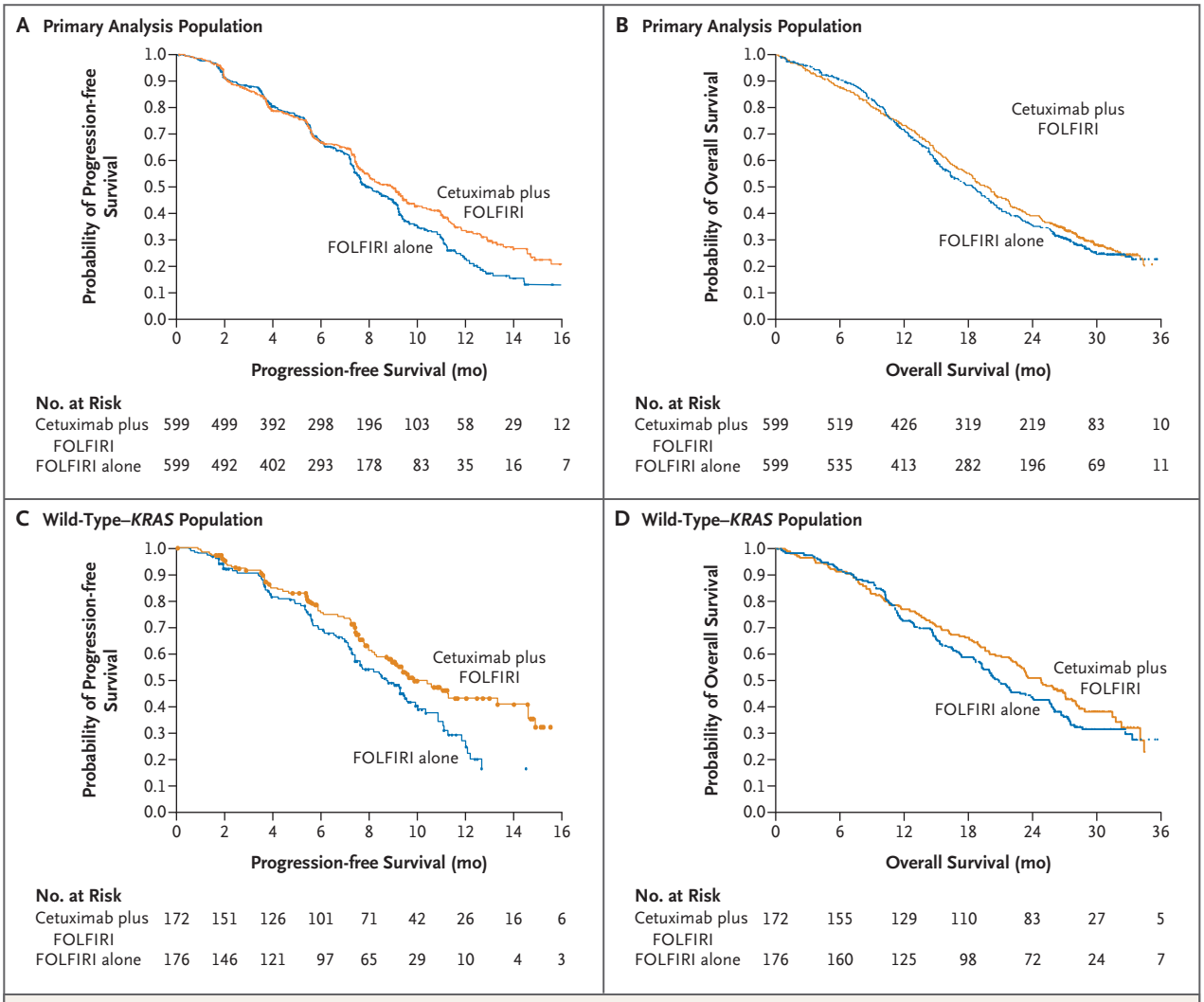

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival in the Primary Analysis Population and the Wild-Type–*KRAS* Population, According to Treatment Group.

Panel A shows progression-free survival among the 1198 patients in the primary analysis population. The hazard ratio for the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% CI, 0.72 to 0.99; P=0.048 by a stratified log-rank test). Median progression-free survival time in the cetuximab–FOLFIRI group was 8.9 months (95% CI, 8.0 to 9.5), as compared with 8.0 months (95% CI, 7.6 to 9.0) in the FOLFIRI group. Panel B shows overall survival among the 1198 patients in the primary analysis population. The hazard ratio for death in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.93 (95% CI, 0.81 to 1.07; P=0.31 by a stratified log-rank test). The median overall survival in the cetuximab–FOLFIRI group was 19.9 months (95% CI, 18.5 to 21.3), as compared with 18.6 months (95% CI, 16.6 to 19.8) in the FOLFIRI group. Panel C shows progression-free survival among the 348 patients with wild-type–*KRAS* tumors. The hazard ratio for progression in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.68 (95% CI, 0.50 to 0.94; P=0.02). The median progression-free survival in the cetuximab–FOLFIRI group was 9.9 months (95% CI, 8.7 to 14.6), as compared with 8.7 months (95% CI, 7.4 to 9.9) in the FOLFIRI group. Panel D shows overall survival among the 348 patients with wild-type–*KRAS* tumors. The hazard ratio for death in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.84 (95% CI, 0.64 to 1.11). The median overall survival in the cetuximab–FOLFIRI group was 24.9 months (95% CI, 22.2 to 27.8), as compared with 21.0 months (95% CI, 19.2 to 25.7) in the FOLFIRI group.

Median overall survival times in the cetuximab–FOLFIRI group and the FOLFIRI group were 24.9 months and 21.0 months, respectively, in the wild-type–*KRAS* population and 17.5 and 17.7 months, respectively, in the mutant-*KRAS* population. Among patients with wild-type–*KRAS* tumors, the response rate in the cetuximab–FOLFIRI group was 59.3% and in the FOLFIRI group 43.2% (odds

Table 2. Efficacy in the Primary Analysis Population, According to Treatment Group.*

Variable	Cetuximab plus FOLFIRI (N=599)	FOLFIRI Alone (N=599)	Hazard Ratio or Odds Ratio (95% CI)†	P Value‡
Progression-free survival				
Progression event — no. (%)	298 (49.7)	322 (53.8)	0.85 (0.72–0.99)	0.048
Months of progression-free survival — median (95% CI)	8.9 (8.0–9.5)	8.0 (7.6–9.0)		
Overall survival				
Deaths — no. (%)	412 (68.8)	416 (69.4)	0.93 (0.81–1.07)	0.31
Months of overall survival — median (95% CI)	19.9 (18.5–21.3)	18.6 (16.6–19.8)		
Response — no. (%)				
Complete response	3 (0.5)	2 (0.3)		
Partial response	278 (46.4)	230 (38.4)		
Stable disease	224 (37.4)	280 (46.7)		
Overall response rate				
No. (%)	281 (46.9)	232 (38.7)	1.40 (1.12–1.77)	0.004
95% CI	42.9–51.0	34.8–42.8		

* FOLFIRI denotes irinotecan, fluorouracil, and leucovorin.
† The ratios listed are hazard ratios, except for the overall response rate, for which the odds ratio is shown.
‡ P values were calculated with the use of the stratified log-rank test or, in the case of the overall response rate, the stratified Cochran–Mantel–Haenszel test.

ratio, 1.91; 95% CI, 1.24 to 2.93) (Fig. 2B). Among those with mutated-*KRAS* tumors, the response rate was 36.2% in the cetuximab–FOLFIRI group and 40.2% in the FOLFIRI group (odds ratio, 0.80; 95% CI, 0.44 to 1.45).

ADVERSE EVENTS

The overall incidence of grade 3 or 4 adverse events was 79.3% in the cetuximab–FOLFIRI group and 61.0% in the FOLFIRI group (P<0.001) (Table 3); the incidence of any such events, excluding skin reactions, was 74.0% in the cetuximab–FOLFIRI group. The administration of cetuximab plus FOLFIRI, as compared with FOLFIRI alone, was associated with significantly more skin reactions (all) (19.7% vs. 0.2%, P<0.001) and acne-like rash (16.2% vs. 0.0%, P<0.001). None of the skin reactions or acne-like rashes reported were grade 4. Median progression-free survival times among patients in the cetuximab–FOLFIRI group were found to increase with an increasing grade of rash. With cetuximab plus FOLFIRI, there was a higher incidence of grade 3 or 4 diarrhea (15.7%, vs. 10.5% with FOLFIRI alone; P=0.008) and infusion-related reactions (2.5% vs. 0.0%, P<0.001), but these effects were able to be managed with protocol-defined treatment modifications. The incidence of treatment-related serious adverse events was 26.0% with cetuximab plus FOLFIRI and 19.3% with FOLFIRI alone. There were no cetuximab-related deaths.

DISCUSSION

We found that the initial treatment of metastatic colorectal cancer with a combination of cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of disease progression by 15% (hazard ratio, 0.85; P=0.048). The addition of cetuximab to FOLFIRI also increased the response rate by nearly 10%. There was no significant difference between the treatment groups in overall survival, however. Treatment added after the conclusion of a study can confound the analysis of overall survival,[26,27] and in this study, approximately two thirds of patients in each group received subsequent chemotherapy after completion of the study, and 25.4% of patients in the FOLFIRI group and 6.2% in the cetuximab–FOLFIRI group received EGFR antibody therapy after the study. Adding cetuximab to FOLFIRI increased the rate of resection of metastases, but whether this increase

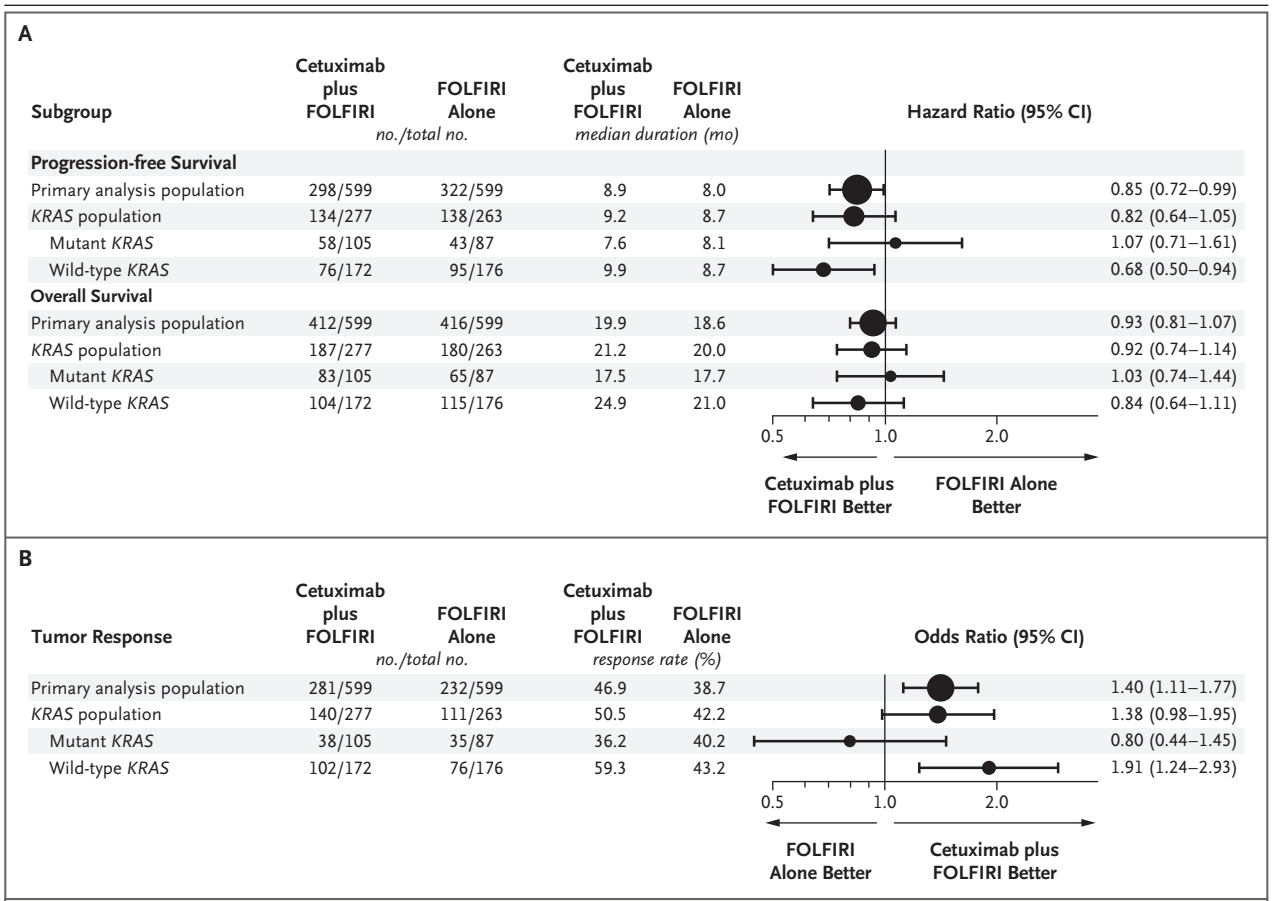

Figure 2. Hazard Ratios for Progression-free and Overall Survival and Odds Ratios with Tumor Response, According to the Mutation Status of *KRAS* in the Tumor.

For the primary analysis population, the hazard ratio for progression-free survival with cetuximab plus FOLFIRI as compared with FOLFIRI alone was significant (P=0.048) (Panel A), as was the odds ratio for tumor response with cetuximab plus FOLFIRI (P=0.004) (Panel B). The interaction between treatment group and *KRAS* mutation status was not significant for progression-free survival (P=0.07) or overall survival (P=0.44) (Panel A) but was significant for response (P=0.03) (Panel B). In both panels, the sizes of the circles are proportional to the numbers of patients.

improves the potential for cure or long-term survival is unknown.

Tumor tissue for the analysis of *KRAS* mutation status was available from approximately half the patients. The incidence of *KRAS* mutations (36%) was in keeping with previous reports.[28,29] There was an interaction between treatment group and *KRAS* status for the response to cetuximab–FOLFIRI (P=0.03) but not for progression-free survival (P=0.07) or overall survival (P=0.44). The hazard ratio for progression-free survival among patients with wild-type–*KRAS* tumors in the cetuximab–FOLFIRI group, as compared with the FOLFIRI group, was 0.68 (95% CI, 0.50 to 0.94), which suggests that the cetuximab–FOLFIRI combination reduces the risk of progression in such patients. The hazard ratio of 0.68 for progression-free survival in this group is consistent with the hazard ratio of 0.57 reported in the randomized, phase 2 OPUS trial (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC trial; ClinicalTrials.gov number, NCT00125034), with cetuximab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX-4) among patients with wild-type–*KRAS* disease.[30] It is also within the range of the hazard ratios for progression-free survival of 0.54 and 0.83 reported in association with combinations of two cytotoxic drugs plus bevacizumab.[31,32] The predictive power of the *KRAS* mutation status of tumors with regard to their responsiveness to cetuximab has been

Table 3. Most Common Grade 3 or 4 Adverse Events and Special Adverse Event Categories in the Safety Population, According to Treatment Group.*

MedDRA Preferred Term†	Cetuximab plus FOLFIRI (N=600)	FOLFIRI Alone (N=602)	P Value
	no. (%)		
Any	476 (79.3)	367 (61.0)	<0.001
Neutropenia‡	169 (28.2)	148 (24.6)	0.16
Leukopenia	43 (7.2)	31 (5.1)	0.15
Diarrhea	94 (15.7)	63 (10.5)	0.008
Fatigue	32 (5.3)	28 (4.7)	0.59
Rash	49 (8.2)	0	<0.001
Dermatitis acneiform	32 (5.3)	0	<0.001
Vomiting	28 (4.7)	30 (5.0)	0.80
Special adverse events			
Skin reactions			
All	118 (19.7)	1 (0.2)	<0.001
Acne-like rash	97 (16.2)	0	<0.001
Infusion-related reaction	15 (2.5)	0	<0.001

* We used retrospective chi-square tests to compare the rates of adverse events between the two treatment groups; the results were not corrected for multiple testing. Under the assumption of no significant difference between the two groups, 11 independent tests and a 0.05 significance level results in a chance of more than 43% of obtaining at least one false positive finding. FOLFIRI denotes irinotecan, fluorouracil, and leucovorin.

† Among the *Medical Dictionary for Regulatory Activities* (MedDRA, version 10.0) preferred terms, no grade 4 reactions were reported for dermatitis acneiform, acne-like rash, or all skin reactions.

‡ Grade 3 or 4 febrile neutropenia was reported in 18 of the 600 patients (3.0%) receiving cetuximab plus FOLFIRI and in 13 of the 602 patients (2.2%) receiving FOLFIRI alone.

shown previously in studies of cetuximab, alone or in combination with irinotecan, administered to patients with metastatic colorectal cancer that had progressed after previous treatment.[13-15,33,34] A similar effect has also been reported in a study of previously treated patients receiving panitumumab in combination with the best supportive care.[18,19]

The safety profile of the cetuximab–FOLFIRI treatment was in line with that expected. The incidence rates of grade 3 or 4 diarrhea, skin reactions, and infusion-related reactions were significantly higher with cetuximab plus FOLFIRI than with FOLFIRI alone, and the overall incidence of grade 3 or 4 adverse events was higher with cetuximab (79.3%, vs. 61.0%; P<0.001). However, these adverse events were generally manageable.

This trial provides confirmation that, as compared with FOLFIRI alone, cetuximab plus FOLFIRI reduces the risk of progression of metastatic colorectal cancer when used as the first-line treatment and that this benefit is seen mainly in patients with wild-type–*KRAS* tumors.

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REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. 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;355:1041-7. [Erratum, Lancet 2000;355:1372.]
3. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 2000;343:905-14.
4. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
5. Van Cutsem E, Geboes K. The multidisciplinary management of gastrointestinal cancer. The integration of cytotoxics and biologicals in the treatment of metastatic colorectal cancer. Best Pract Res Clin Gastroenterol 2007;21:1089-108.
6. 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;351:337-45.
7. Lenz HJ, Van Cutsem E, Khambata-Ford S, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol 2006;24:4914-21.
8. Folprecht G, Lutz MP, Schöffski P, et al. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. Ann Oncol 2006;17:450-6.
9. Rougier P, Raoul J-L, Van Laethem J-L, et al. Cetuximab + FOLFIRI as first-line treatment for metastatic colorectal CA. J Clin Oncol 2004;22:Suppl:248s. abstract.
10. Tabernero J, Van Cutsem E, Diaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2007;25:5225-32.
11. Bokemeyer C, Staroslawska E, Makhson A, et al. Cetuximab plus 5FU/FA/oxaliplatin (FOLFOX4) in the first-line treatment of metastatic colorectal cancer (mCRC): a large-scale phase II study, OPUS. Eur J Cancer Suppl 2007;5:236. abstract.
12. Arnold D, Höhler T, Dittrich C, et al. Cetuximab in combination with weekly 5-fluorouracil/folinic acid and oxaliplatin (FUFOX) in untreated patients with advanced colorectal cancer: a phase Ib/II study of the AIO GI Group. Ann Oncol 2008;19:1442-9.
13. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008;19:508-15.
14. Di Fiore F, Blanchard F, Charbonnier F, et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 2007;96:1166-9.
15. Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26:374-9.
16. Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006;66:3992-5.
17. Cervantes A, Macarulla T, Martinelli E, et al. Correlation of KRAS status (wild type [wt] vs. mutant [mt]) with efficacy to first-line cetuximab in a study of cetuximab single agent followed by cetuximab + FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 2008;26:Suppl:210s. abstract.
18. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-64.
19. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626-34.
20. 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;22:229-37.
21. Chen CY, Shiesh SC, Wu SJ. Rapid detection of K-ras mutations in bile by peptide nucleic acid-mediated PCR clamping and melting curve analysis: comparison with restriction fragment length polymorphism analysis. Clin Chem 2004;50:481-9.
22. Simeonov A, Nikiforov TT. Single nucleotide polymorphism genotyping using short, fluorescently labeled locked nucleic acid (LNA) probes and fluorescence polarization detection. Nucleic Acids Res 2002;30(17):e91.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
24. Collett D. Modelling survival data in medical research. 2nd ed. Boca Raton, FL: Chapman and Hall, 2003.
25. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley, 1981.
26. Food and Drug Administration. Clinical trial endpoints for the approval of cancer drugs and biologics. (Accessed March 9, 2009, at http://www.fda.gov/CBER/gdlns/clintrialend.pdf.)
27. Schilsky RL. End points in cancer clinical trials and the drug approval process. Clin Cancer Res 2002;8:935-8.
28. McLellan EA, Owen RA, Stepniewska KA, Sheffield JP, Lemoine NR. High frequency of K-ras mutations in sporadic colorectal adenomas. Gut 1993;34:392-6.
29. Arber N, Shapira I, Ratan J, et al. Activation of c-K-ras mutations in human gastrointestinal tumors. Gastroenterology 2000;118:1045-50.
30. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-7.
31. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
32. Saltz LB, Clarke S, 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;26:2013-9.
33. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-7.
34. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-65.