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Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer

Jolien Tol, M.D., Miriam Koopman, M.D., Annemieke Cats, M.D., Ph.D., Cees J. Rodenburg, M.D., Ph.D., Geert J.M. Creemers, M.D., Ph.D., Jolanda G. Schrama, M.D., Frans L.G. Erdkamp, M.D., Ph.D., Allert H. Vos, M.D., Cees J. van Groeningen, M.D., Ph.D., Harm A.M. Sinnige, M.D., Ph.D., Dirk J. Richel, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Jeroen R. Dijkstra, B.Sc., Marianne E. Vink-Börger, M.Sc., Ninja F. Antonini, M.Sc., Linda Mol, M.Sc., Johan H.J.M. van Krieken, M.D., Ph.D., Otilia Dalesio, M.Sc., and Cornelis J.A. Punt, M.D., Ph.D.

ABSTRACT

BACKGROUND

Fluoropyrimidine-based chemotherapy plus the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab is standard first-line treatment for metastatic colorectal cancer. We studied the effect of adding the anti–epidermal growth factor receptor (EGFR) antibody cetuximab to a combination of capecitabine, oxaliplatin, and bevacizumab for metastatic colorectal cancer.

METHODS

We randomly assigned 755 patients with previously untreated metastatic colorectal cancer to capecitabine, oxaliplatin, and bevacizumab (CB regimen, 378 patients) or the same regimen plus weekly cetuximab (CBC regimen, 377 patients). The primary end point was progression-free survival. The mutation status of the *KRAS* gene was evaluated as a predictor of outcome.

RESULTS

The median progression-free survival was 10.7 months in the CB group and 9.4 in the CBC group (P=0.01). Quality-of-life scores were lower in the CBC group. The overall survival and response rates did not differ significantly in the two groups. Treated patients in the CBC group had more grade 3 or 4 adverse events, which were attributed to cetuximab-related adverse cutaneous effects. Patients treated with cetuximab who had tumors bearing a mutated *KRAS* gene had significantly decreased progression-free survival as compared with cetuximab-treated patients with wild-type–*KRAS* tumors or patients with mutated-*KRAS* tumors in the CB group.

CONCLUSIONS

The addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab resulted in significantly shorter progression-free survival and inferior quality of life. Mutation status of the *KRAS* gene was a predictor of outcome in the cetuximab group. (ClinicalTrials.gov number, NCT00208546.)

From Radboud University Nijmegen Medical Center, Nijmegen (J.T., M.K., J.R.D., M.E.V.-B., J.H.J.M.K., C.J.A.P.); the Netherlands Cancer Institute, Amsterdam (A.C., N.F.A., O.D.); Meander Medical Center, Amersfoort (C.J.R.); Catharina Hospital, Eindhoven (G.J.M.C.); Spaarne Hospital, Hoofddorp (J.G.S.); Maasland Hospital, Sittard (F.L.G.E.); Bernhoven Hospital, Oss (A.H.V.); the Free University Medical Center, Amsterdam (C.J.G.); Jeroen Bosch Hospital, 's-Hertogenbosch (H.A.M.S.); the Amsterdam Medical Center, Amsterdam (D.J.R.); University Medical Center, Utrecht (E.E.V.); and the Comprehensive Cancer Center East, Nijmegen (L.M.) — all in the Netherlands. Address reprint requests to Dr. Punt at the Department of Medical Oncology, Radboud University Nijmegen Medical Center, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands, or at c.punt@onco.umcn.nl.

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Fluoropyrimidines (e.g., fluorouracil and capecitabine), irinotecan, and oxaliplatin are the standard cytotoxic drugs used in treating metastatic colorectal cancer.[1,2] The combination of capecitabine and oxaliplatin is similar to the combination of fluorouracil and oxaliplatin in efficacy and safety.[3,4] Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF),[5-7] combined with fluoropyrimidine-based chemotherapy is now the standard first-line treatment for metastatic colorectal cancer. Cetuximab, a chimeric IgG1 monoclonal antibody against epidermal growth factor receptor (EGFR), has efficacy as monotherapy and in combination with irinotecan in irinotecan-resistant patients.[8,9] We prospectively evaluated the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab as first-line treatment in patients with metastatic colorectal cancer (the CAIRO2 trial).

Methods

Patients

Eligible patients were older than 18 years of age, had histologically proved colon or rectal carcinoma, metastatic disease not amenable to curative surgery, measurable tumor, no previous systemic chemotherapy for metastatic disease, World Health Organization (WHO) performance status 0 or 1, no adjuvant chemotherapy within 6 months before randomization, and adequate bone marrow, liver, and renal function. We excluded patients if they had higher than grade 1 sensory neuropathy, previous intolerance of adjuvant chemotherapy, symptomatic central nervous system metastases, bleeding diathesis, coagulation disorders, clinically significant cardiovascular disease, or other cancers within the previous 5 years, except for adequately treated squamous or basal-cell carcinoma of the skin or carcinoma in situ of the cervix.

Study Design

This open-label, randomized, phase 3 trial was conducted in 79 centers in the Netherlands. Eligible patients were randomly assigned at a 1:1 ratio to receive treatment with or without cetuximab. Randomization was performed centrally by a minimization technique with stratification according to serum lactate dehydrogenase level (normal or abnormal, according to the cutoff values of each individual center), previous adjuvant chemotherapy (yes or no), number of affected organs (one or more than one), and treatment center. The study was approved by the Committee on Human-Related Research Arnhem–Nijmegen and by the local institutional review boards. An independent data and safety monitoring committee evaluated all serious adverse events. All patients provided written informed consent before study entry.

Bevacizumab was donated by Roche, and cetuximab was donated by Merck Serono. The sponsors of the study were informed of the results of the study but did not contribute to any phase of the study design; the collection, analysis, and interpretation of the data; or the writing of the manuscript.

Treatment and Testing

Treatment for the capecitabine–bevacizumab (CB) group consisted of 1000 mg of capecitabine per square meter of body-surface area, given orally twice daily on days 1 to 14; 130 mg of oxaliplatin per square meter, given intravenously on day 1; and 7.5 mg of bevacizumab per kilogram of body weight, given intravenously on day 1. Treatment for the capecitabine–bevacizumab–cetuximab (CBC) group consisted of the same regimen of capecitabine, oxaliplatin, and bevacizumab plus 400 mg of cetuximab per square meter, given intravenously on day 1 of the first treatment cycle, followed by 250 mg of cetuximab per square meter given weekly thereafter. All treatment cycles were administered every 3 weeks. In both treatment groups, oxaliplatin was administered for a maximum of six cycles to prevent serious peripheral sensory neurotoxicity, and from cycle 7 the dose of capecitabine was increased to 1250 mg per square meter.

Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Dose reductions because of adverse events were performed for each agent as specified in the study protocol. A cetuximab-related adverse cutaneous effect was defined as any adverse cutaneous effect with the exception of hand–foot syndrome. Central review was performed of the charts of all patients who died within 30 days after the last administration of the study drugs and whose death was accompanied by any event other than disease progression, regardless of the reported cause. The results of the central review were submitted to the independent data and safety

monitoring committee for final assessment. An interim analysis of safety in the first 400 patients has been published.[10]

Tumor response was assessed by the local investigators every 9 weeks with the use of computed tomographic scans, according to the Response Evaluation Criteria in Solid Tumors (RECIST).[11] The overall response rate was defined as the rate of all responses, including complete and partial responses. Disease control was defined as complete response, partial response, or stable disease as the best response. Treatment was continued until the occurrence of disease progression, death, or unacceptable adverse event, whichever came first. Patients whose treatment was discontinued for reasons other than disease progression were evaluated for a response every 3 months. The relative dose intensity was defined as the ratio of the dose administered to the planned dose. Quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire at baseline within 2 weeks before randomization and every 9 weeks thereafter until the end of the study treatment.

Formalin-fixed, paraffin-embedded tumor material was collected from patients for whom resected primary tumor tissue was available. DNA was extracted from tumor tissue for mutation analysis of the *KRAS* gene (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

EGFR expression was determined by immunohistochemical assay on tissue microarrays with the use of the EGFR pharmDx Kit (Dako) according to the manufacturer's instructions. Powervision (Immunologic) was used as a visualization method. In accordance with the pharmDx Kit guidelines, tumors showing more than 1% membranous EGFR stained cells were considered positive.

STATISTICAL ANALYSIS

The primary end point was progression-free survival, which was defined as the interval from the date of randomization to the date of disease progression, death, or last follow-up, whichever occurred first. It was estimated that with 540 events (progression or death), a two-sided log-rank test at a significance level of 5% would have a power of 80% to detect a difference in median progression-free survival of 11 to 14 months (hazard ratio, 0.79). On the assumption of an accrual and follow-up period of 36 months, we planned to include approximately 750 patients in the study. The secondary end points were overall survival, safety, response rate, quality of life, and the influence of *KRAS* mutational status and expression of EGFR in tumor samples on the outcome. Ineligible patients or patients who withdrew informed consent were excluded from all analyses. Data from eligible patients were analyzed according to the intention-to-treat principle, and these patients remained in follow-up until disease progression occurred. Data from patients who were alive without recurrence at the time of analysis were censored. The progression-free and overall survival curves were estimated by the Kaplan–Meier method and compared by means of the log-rank test. We performed a multivariate analysis using a Cox proportional-hazards model with treatment group, serum lactate dehydrogenase level, number of affected organs, and previous adjuvant chemotherapy as covariables.

Patients who started treatment were evaluated for adverse events, and patients who completed at least three cycles were evaluated for response. The worst grade of adverse event was compared between the treatment groups with the use of the chi-square test. The correlation between cetuximab-related adverse cutaneous effects and survival was assessed in a landmark-type analysis. Patients who started treatment were grouped according to the worst grade of cetuximab-related adverse cutaneous effect reported during the first six cycles. The Wilcoxon rank-sum test was used to detect statistically significant differences between the treatment groups in the change in the mean quality-of-life score. Patients who completed the quality-of-life questionnaire at baseline and at least once during treatment were evaluated. All analyses were performed with the use of SAS software, version 9.1.

RESULTS

PATIENTS

Between June 2005 and December 2006, 755 patients underwent randomization: 378 to receive treatment without cetuximab (CB group) and 377 to receive treatment with cetuximab (CBC group). Nineteen patients (2.5%) were ineligible (Supplementary Appendix). The study was completed according to the protocol, and the estimated number of events occurred. The baseline characteristics of all 736 eligible patients (368 in each treatment

group) were well matched between the two groups except for sex (Table 1). The median duration of follow-up at the time of this analysis was 23 months.

TREATMENT

Treatment was started in 732 eligible patients, 366 in each group. The Supplementary Appendix gives the median and mean numbers of treatment cycles, the median duration of treatment, and the median relative dose intensity.

The reasons for discontinuation of treatment in the CB group (313 patients) and the CBC group (334 patients) were progression of disease (169 patients [54.0%] and 162 patients [48.5%], respectively; P=0.16), adverse events (81 [25.9%] and 99 [29.6%], P=0.28), resection of metastases (13 [4.2%] and 18 [5.4%], P=0.46), and declining of treatment by the patient (19 [6.1%] and 25 [7.5%], P=0.48). All study drugs were discontinued in 12 patients in the CBC group for adverse events that appeared to be related exclusively to cetuximab. A total of 345 of all 736 eligible patients (46.9%) received further systemic treatment after disease progression: 168 in the CB group (45.7%) and 177 in the CBC group (48.1%). Of these patients, 48 received oxaliplatin (18 in the CB group and 30 in the CBC group), 278 received irinotecan (144 and 134, respectively), and 22 received cetuximab (15 and 7); cetuximab was usually administered in combination with irinotecan.

EFFICACY

The primary end point was reached in 293 patients in the CB group and 316 patients in the CBC group. The addition of cetuximab significantly decreased the median progression-free survival (10.7 months in the CB group and 9.4 months in the CBC group, P=0.01) (Table 2 and Fig. 1A). The

Table 1. Baseline Characteristics of the Patients.*

Characteristic	CB Group (N=368)	CBC Group (N=368)	P Value
Age — yr			0.95
Median	62	62	
Range	27–83	33–80	
Sex — no. (%)			0.04
Male	205 (55.7)	233 (63.3)	
Female	163 (44.3)	135 (36.7)	
WHO performance status — no. (%)			0.09
0	219 (59.5)	240 (65.2)	
1	149 (40.5)	126 (34.2)	
No data		2 (0.5)	
Serum lactate dehydrogenase level — no. (%)			0.82
Normal	210 (57.1)	207 (56.2)	
Above normal	158 (42.9)	161 (43.8)	
Previous adjuvant therapy — no. (%)	55 (14.9)	56 (15.2)	0.92
Site of primary tumor — no. (%)			0.50
Colon	164 (44.6)	172 (46.7)	
Rectum	108 (29.3)	94 (25.5)	
Rectosigmoid	96 (26.1)	102 (27.7)	
No. of affected organs — no. (%)			0.77
1	167 (45.4)	163 (44.3)	
>1	201 (54.6)	205 (55.7)	

* CB denotes capecitabine, oxaliplatin, and bevacizumab, CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab, and WHO World Health Organization. Because of rounding, not all percentages total 100.

hazard ratio for disease progression or death in the CBC group was 1.22 (95% confidence interval, 1.04 to 1.43). In a multivariate analysis, an elevated serum lactate dehydrogenase level (P<0.001) and treatment group (P=0.03) correlated significantly with progression-free survival. The median overall survival was 20.3 months in the CB group and 19.4 months in the CBC group (P=0.16) (Table 2 and Fig. 1B). A total of 407 patients died, 193 in the CB group and 214 in the CBC group. The rate of death from any cause at 60 days was 1.9% in the CB group and 2.7% in the CBC group. The overall response rate in the 649 patients who were evaluated was 50.0% in the CB group and 52.7% in the CBC group (P=0.49). Disease control was observed in 94.0% of the patients in the CB group and 94.6% of those in the CBC group (P=0.72).

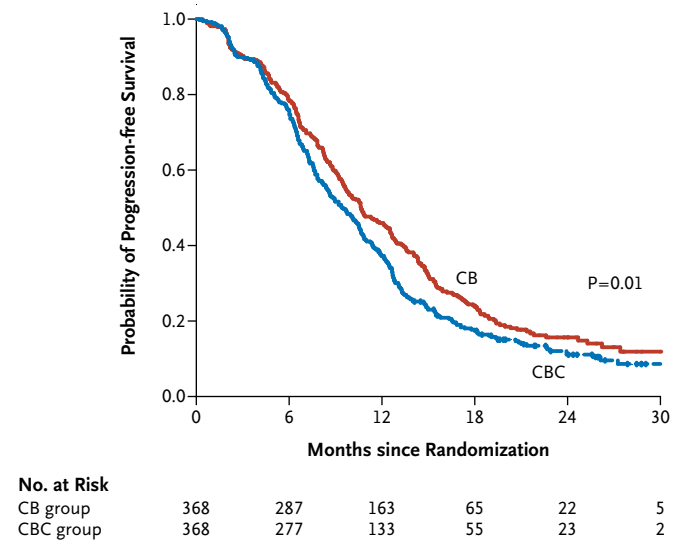
SUBGROUP ANALYSES

The mutation status of the *KRAS* gene was evaluated in 528 tumors (Table 3). Eight samples were excluded because of discordance in the results of the two test methods. An activating *KRAS* mutation was found in 206 tumors (39.6%): 108 from patients in the CB group and 98 from patients in the CBC group. The baseline characteristics were well balanced between patients with wild-type–*KRAS* tumors and those with mutated-*KRAS* tumors (data not shown). Cetuximab-treated patients with mutated-*KRAS* tumors had significantly shorter progression-free survival than cetuximab-treated patients with wild-type–*KRAS* tumors (8.1 vs. 10.5 months, P=0.04) (Fig. 2A). As compared with patients with mutated-*KRAS* tumors in the CB group, cetuximab-treated patients with mutated-*KRAS* tumors had significantly shorter progression-free survival (8.1 vs. 12.5 months, P=0.003) and overall survival (17.2 vs. 24.9 months, P=0.03). Among patients with wild-type–*KRAS* tumors, there was no significant difference in progression-free survival between the two treatment groups. Among patients treated with cetuximab, the response rate was significantly lower in those with *KRAS* mutations than in those with wild-type–*KRAS* tu-

Table 2. Efficacy of Study Treatment.*

Outcome	CB Group (N=368)	CBC Group (N=368)	P Value
Progression-free survival (mo)			0.01
Median	10.7	9.4	
95% CI	9.7–12.3	8.4–10.5	
Overall survival (mo)			0.16
Median	20.3	19.4	
95% CI	17.8–24.7	17.5–21.4	
Response rate (%)†	50.0	52.7	0.49
Disease control rate (%)†	94.0	94.6	0.72
No. of treatment cycles			0.009
Median	10	9	
Range	1–44	1–44	
Duration of treatment (mo)			<0.001
Median	7	6	
Range	1–31	1–33	
Primary reason for treatment discontinuation (%)			
Disease progression	54.0	48.5	0.16
Adverse events	25.9	29.6	0.28
Other	20.1	21.9	0.59
60-Day mortality (%)	1.9	2.7	0.46

* CB denotes capecitabine, oxaliplatin, and bevacizumab, CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab, and CI confidence interval.
† A total of 649 patients (332 in the CB group and 317 in the CBC group) were evaluated for response.



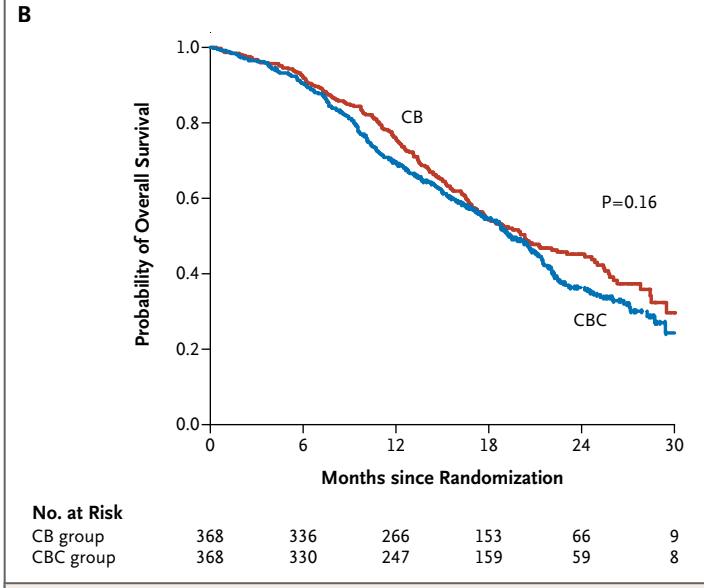


Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.
Panel A shows progression-free survival; the median was 9.4 months in the group receiving capecitabine, oxaliplatin, and bevacizumab plus cetuximab (CBC) and 10.7 months in the group receiving the same regimen without cetuximab (CB), corresponding to a hazard ratio of 1.22 (P=0.01). Panel B shows overall survival; the median was 19.4 months in the CBC group and 20.3 months in the CB group (P=0.16; hazard ratio, 1.15).

mors (45.9% vs. 61.4%, P=0.03), whereas no significant difference was observed in the CB group (59.2% vs. 50.0%, P=0.16).

EGFR was evaluated in 496 tumors, of which 315 (63.5%) tested positive. The baseline characteristics were not significantly different between EGFR-positive and EGFR-negative patients (data not shown). Among EGFR-positive patients, the median progression-free survival was 12.2 months in the CB group and 9.8 months in the CBC group (P=0.003). We did not observe a significant correlation between *KRAS* mutation status or EGFR expression and the incidence of cetuximab-related adverse cutaneous effects (data not shown).

As compared with women in the CBC group, women who were assigned to the CB group had significantly better progression-free survival (12.5 vs. 8.6 months, P<0.001) and overall survival (20.1 vs. 18.8 months, P=0.02). However, these differences were not observed in men. The distribution of baseline characteristics was similar in women and men. In a multivariate analysis, the interaction between sex and treatment group was statistically significant for progression-free survival (P=0.005) but not for overall survival (P=0.10).

The severity of cetuximab-related adverse cutaneous effects correlated significantly with progression-free survival (P<0.001) (Fig. 2B). The median progression-free survival in patients with grade 0 or 1, patients with grade 2, and patients with grade 3 cetuximab-related adverse cutaneous effects was 7.8 months, 10.2 months, and 11.4 months, respectively. The progression-free survival did not differ significantly between patients in the CB group and patients with grade 3 cetuximab-related adverse cutaneous effects in the CBC group (P=0.72).

SAFETY

Table 4 and the Supplementary Appendix list the most frequently observed grade 3 or 4 adverse events. The incidence of any grade 3 or 4 adverse event was 73.2% in the CB group and 81.7% in the CBC group (P=0.006). When grade 3 cetuximab-related adverse cutaneous effects were excluded from this analysis, the incidence was similar: 73.2% in the CB group and 74.3% in the CBC group (P=0.74).

QUALITY OF LIFE

A total of 532 patients (276 in the CB group and 256 in the CBC group) were evaluated for quality of life. Overall quality of life and global health status were similar in the two groups at baseline; during treatment, both measures improved significantly more in the CB group than in the CBC group (P=0.007 and P=0.03, respectively). The mean increase in global health status was 0.4

point in the CB group and 0.0 points in the CBC group (P=0.007). There were no significant differences between the treatment groups in the change from baseline in scores for pain, financial problems, and decrease in functioning (physical, emotional, cognitive, and social).

DISCUSSION

In this randomized trial conducted in previously untreated patients with metastatic colorectal cancer, the addition of cetuximab to treatment with capecitabine, oxaliplatin, and bevacizumab resulted in a significant decrease in progression-free survival and a poorer quality of life. The reduction in progression-free survival was unexpected, since preclinical as well as early clinical studies suggested a benefit from the combination of anti-VEGF and anti-EGFR antibodies.[12-15] An increase in adverse events is an unlikely cause of the reduction in progression-free survival, since such events were manageable and the percentage of patients who discontinued treatment because of adverse events was similar in the two treatment groups. A similar result with anti-EGFR therapy was observed in the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial,[16,17] in which previously untreated patients with metastatic colorectal cancer were randomly assigned to fluorouracil, leucovorin, bevacizumab, and irinotecan or oxaliplatin, with or without panitumumab, a human antibody against EGFR. The PACCE trial was prematurely discontinued because of decreased progression-free survival and increased adverse events in the panitumumab group, but the decrease in progression-free survival was observed only in patients who were treated with oxaliplatin. The Bowel Oncology with Cetuximab Antibody (BOND) 2 trial showed efficacy in treatment with irinotecan, bevacizumab, and cetuximab in patients with irinotecan-resistant colorectal cancer,[18] a result that suggested a higher response rate and longer progression-free survival than was found in a previous trial (BOND) of irinotecan and cetuximab in similar patients.[9] Preliminary results of chemotherapy with or without cetuximab in the first-line treatment of metastatic colorectal cancer indicate somewhat better progression-free survival with irinotecan than with oxaliplatin,[19,20] but these comparisons should be interpreted with caution: whether cetuximab is more efficacious when given in combination with irinotecan than with oxaliplatin remains speculative.

Table 3. Association of the Mutation Status of the *KRAS* Gene with Progression-free Survival, Overall Survival, and Response Rate.*

Variable	Wild-Type *KRAS*	Mutated *KRAS*	P Value
No. of patients			
CB group	156	108	
CBC group	158	98	
Median progression-free survival (mo)			
CB group	10.6	12.5	0.80
CBC group	10.5	8.1	0.04
P value	0.30	0.003	
Median overall survival (mo)			
CB group	22.4	24.9	0.82
CBC group	21.8	17.2	0.06
P value	0.64	0.03	
Response rate (%)			
CB group	50.0	59.2	0.16
CBC group	61.4	45.9	0.03
P value	0.06	0.03	

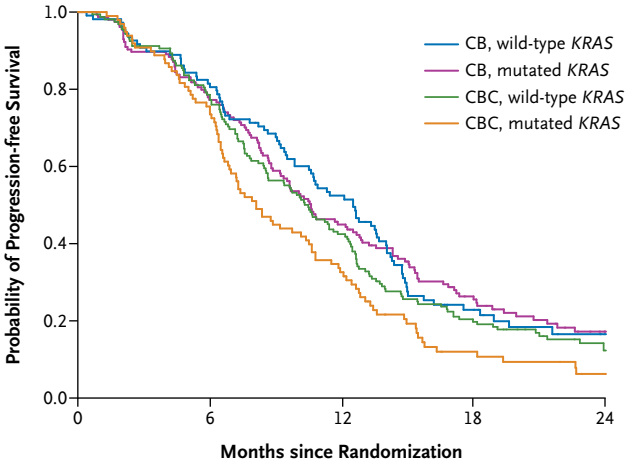
* CB denotes capecitabine, oxaliplatin, and bevacizumab, and CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab.

The results of our trial might be due to a negative interaction between cetuximab and bevacizumab. Hypertension, a common side effect of bevacizumab treatment, was recently shown to correlate with clinical outcome in patients with colorectal cancer.[21] Our observation that hypertension was less frequent in the CBC group suggests decreased efficacy of bevacizumab when administered in combination with cetuximab. In contrast, preclinical studies have suggested a positive interaction between VEGF- and EGFR-inhibiting agents.[12-15] However, to our knowledge, the combination of cetuximab and bevacizumab has not been tested in this setting.

The severity of cetuximab-related adverse cutaneous effects correlated directly and significantly with progression-free survival, but the median progression-free survival among patients with the most severe cetuximab-related adverse cutaneous effects was not significantly better than that among patients treated without cetuximab.

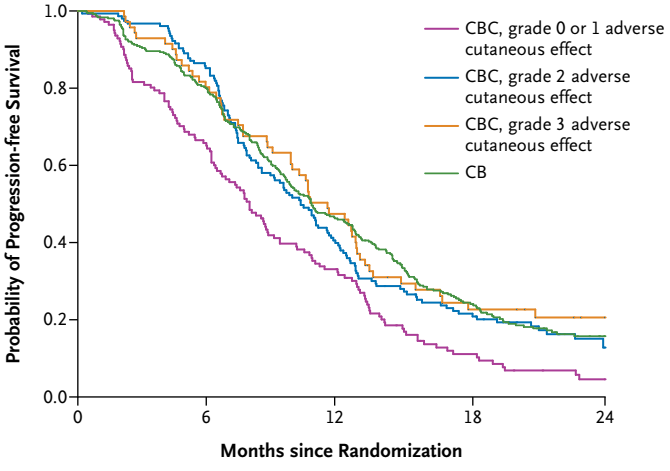
Women treated with cetuximab had shorter progression-free survival than women treated

A



No. at Risk					
CB, wild-type *KRAS*	155	118	67	32	11
CB, mutated *KRAS*	108	88	54	18	7
CBC, wild-type *KRAS*	159	124	67	30	13
CBC, mutated *KRAS*	98	74	31	9	3

B



No. at Risk					
CBC, grade 0 or 1 adverse cutaneous effect	141	89	42	13	4
CBC, grade 2 adverse cutaneous effect	155	132	58	29	11
CBC, grade 3 adverse cutaneous effect	71	56	33	13	8
CB	366	286	163	65	22

Figure 2. Kaplan–Meier Estimates of Progression-free Survival According to *KRAS* Mutation Status and Cetuximab-Related Adverse Cutaneous Effects.

Among patients in the group receiving capecitabine, oxaliplatin, and bevacizumab plus cetuximab (CBC), the median progression-free survival was significantly decreased when their tumor harbored a *KRAS* mutation (8.1 vs. 10.5 months, P=0.04) (Panel A). Among patients with mutated-*KRAS* tumors, the median progression-free survival was significantly decreased in the CBC group as compared with the group receiving capecitabine, oxaliplatin, and bevacizumab (CB) (8.1 vs. 12.5 months, P=0.003). In the CBC group, the median progression-free survival in treated patients with grade 0 or 1, treated patients with grade 2, and treated patients with grade 3 cetuximab-related adverse cutaneous effects was 7.8 months, 10.2 months, and 11.4 months, respectively (P<0.001) (Panel B). The difference between patients with grade 3 adverse cutaneous effects in the CBC group and patients in the CB group was not statistically significant (P=0.72).

without cetuximab, but this difference was not found in men. Women also had a lower incidence of grade 3 cetuximab-related adverse cutaneous effects, which might indicate a decreased efficacy of cetuximab in our study. Although the management of adverse cutaneous effects may be different in women than in men, with earlier discontinuation of cetuximab in women for cosmetic reasons, this would not explain the poorer results in the CBC group.

The *KRAS* genotype affects the response to anti-EGFR treatment: patients with wild-type–*KRAS* tumors have longer progression-free survival than those with mutated-*KRAS* tumors.[22-26] The results of our study also confirm the role of the mutation status of the *KRAS* gene in the response to cetuximab when cetuximab is administered in combination with chemotherapy and bevacizumab as first-line treatment. We observed the worst result for progression-free survival in patients with mutated-*KRAS* tumors who were treated with cetuximab. A similar result was found in trials of chemotherapy with or without cetuximab as first-line treatment of metastatic colorectal cancer.[25,26]

Many targeted agents are available or under development for use in a wide range of tumors. The inhibition of a single signal-transduction pathway is unlikely to provide optimal results, and therefore a combination of agents appears to be a valid strategy. Our results, however, argue against the combined use of anti-VEGF and anti-EGFR monoclonal antibodies with chemotherapy in cases of metastatic colorectal cancer.

Table 4. Serious Adverse Events.*

Event	CB Group (N=366)	CBC Group (N=366)	P Value
	number (percent)		
Any grade 3 or 4 event	268 (73.2)	299 (81.7)	0.006
Adverse cutaneous effects			
Any event	76 (20.8)	143 (39.1)	<0.001
Acneiform rash	2 (0.5)	93 (25.4)	<0.001
Hand–foot skin reaction	71 (19.4)	68 (18.6)	0.78
Diarrhea	70 (19.1)	95 (26.0)	0.03
Nausea	31 (8.5)	23 (6.3)	0.26
Vomiting	30 (8.2)	22 (6.0)	0.25
Fatigue	48 (13.1)	55 (15.0)	0.46
Sensory neuropathy	38 (10.4)	28 (7.7)	0.20
Infection	25 (6.8)	22 (6.0)	0.65
Neutropenic fever	5 (1.4)	3 (0.8)	0.48
Hypersensitivity reaction	15 (4.1)	18 (4.9)	0.59
Hypertension	54 (14.8)	34 (9.3)	0.02
Gastrointestinal perforation	1 (0.3)	6 (1.6)	0.06
Bleeding	6 (1.6)	2 (0.5)	0.16
Venous thromboembolic events	25 (6.8)	30 (8.2)	0.48
Arterial thromboembolic events	12 (3.3)	8 (2.2)	0.26

* CB denotes capecitabine, oxaliplatin, and bevacizumab, and CBC capecitabine, oxaliplatin, and bevacizumab plus cetuximab.

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APPENDIX

The team members of the CAIRO2 trial are as follows: Medical Oncology Task Force of the Dutch Colorectal Cancer Group: E. Balk, J.W.R. Nortier, A. Cats, C.J.A. Punt, C.J. van Groeningen, D.J. Richel, R.L.H. Jansen, H.P. Sleeboom, J.J.M. van der Hoeven, J. Verweij, A.S.T. Planting, R.S. de Jong, E.E. Voest, N.H. Mulder; in addition, the following investigators in the Netherlands participated in the study: Alkmaar — C. Smorenburg; Almelo — R. Hoekstra; Amersfoort — C. Rodenburg; Amstelveen — J. van der Hoeven; Amsterdam — A. Cats, M. Geenen, C. van Groeningen, D. Richel, B. de Valk, N. Weijl; Arnhem — J. Douma; Assen — P. Nieboer; Bergen op Zoom — F. Valster; Beverwijk — R. Rietbroek; Blaricum — A. Ten Tije; Breda — O. Loosveld; Capelle a/d IJssel — D. Kehrer; Delft — M. Bos; Delfzijl — Z. Erjavec; Den Bosch — H. Sinnige, C. Knibbeler; Den Haag — W. Van Deijk, F. Jeurissen, H. Sleeboom; Deventer — A. Imholz; Doetinchem — E. Muller; Dordrecht — J. vanden Bosch; Drachten — S. Hovenga; Ede — E. Balk; Eindhoven — G. Creemers, M. Dercksen; Enschede — M. Legdeur; Geldrop — A. Smals; Goes — H. van Halteren; Gorinchem — M. van Hennik; Gouda — A. van der Torren; Groningen — G. Hospers, R. de Jong; Haarlem — G. de Klerk; Harderwijk — P. Zoon; Heerlen — J. Wals; Helmond — V. Derleyn; Hengelo — H. Dankbaar; Hilversum — S. Luyckx; Hoofddorp — C. de Swart; Hoogeveen — J. Haasjes; Hoorn — W. Meijer; Leeuwarden — M. Polee; Leiden — M. Tesselaar; Leidschendam — H. Oosterkamp; Lelystad — J. Bollen; Maastricht

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