ORIGINAL ARTICLE

Cetuximab for the Treatment of Colorectal Cancer

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ABSTRACT

BACKGROUND

Cetuximab, an IgG1 chimeric monoclonal antibody against epidermal growth factor receptor (EGFR), has activity against colorectal cancers that express EGFR.

METHODS

From December 2003 to August 2005, 572 patients who had colorectal cancer expressing immunohistochemically detectable EGFR and who had been previously treated with a fluoropyrimidine, irinotecan, and oxaliplatin or had contraindications to treatment with these drugs underwent randomization to an initial dose of 400 mg of cetuximab per square meter of body-surface area followed by a weekly infusion of 250 mg per square meter plus best supportive care (287 patients) or best supportive care alone (285 patients). The primary end point was overall survival.

RESULTS

In comparison with best supportive care alone, cetuximab treatment was associated with a significant improvement in overall survival (hazard ratio for death, 0.77; 95% confidence interval [CI], 0.64 to 0.92; P=0.005) and in progression-free survival (hazard ratio for disease progression or death, 0.68; 95% CI, 0.57 to 0.80; P<0.001). These benefits were robust after adjustment in a multivariable Cox proportional-hazards model. The median overall survival was 6.1 months in the cetuximab group and 4.6 months in the group assigned to supportive care alone. Partial responses occurred in 23 patients (8.0%) in the cetuximab group but in none in the group assigned to supportive care alone (P<0.001); the disease was stable in an additional 31.4% of patients assigned to cetuximab and in 10.9% of patients assigned to supportive care alone (P<0.001). Quality of life was better preserved in the cetuximab group, with less deterioration in physical function and global health status scores (both P<0.05). Cetuximab treatment was associated with a characteristic rash; a rash of grade 2 or higher was strongly associated with improved survival (hazard ratio for death, 0.33; 95% CI, 0.22 to 0.50; P<0.001). The incidence of any adverse event of grade 3 or higher was 78.5% in the cetuximab group and 59.1% in the group assigned to supportive care alone (P<0.001).

CONCLUSIONS

Cetuximab improves overall survival and progression-free survival and preserves quality-of-life measures in patients with colorectal cancer in whom other treatments have failed. (ClinicalTrials.gov number, NCT00079066.)

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Colorectal cancer has a worldwide annual incidence of 917,000 and is the second leading cause of cancer-related death in Western nations.[1] The cytotoxic agents irinotecan, oxaliplatin, and the fluoropyrimidines, as well as bevacizumab, the antibody against vascular endothelial growth factor A, have increased the median survival of patients with advanced colorectal cancer,[2-9] but in most patients the disease is incurable.

Recent advances have led to the development of agents that specifically inhibit tumor growth. Epidermal growth factor receptor (EGFR) is often up-regulated in colorectal cancer. Cetuximab, a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of EGFR, blocks ligand-induced receptor signaling and modulates tumor-cell growth. Immune-mediated antitumor mechanisms, such as antibody-dependent cell-mediated cytotoxicity, may also contribute to the activity of cetuximab.[10,11] Cetuximab has activity in colorectal cancer[12] and can reverse drug resistance in patients with colorectal cancer when administered with irinotecan.[13,14] However, to our knowledge, no trials have demonstrated an effect of cetuximab on survival or quality of life in patients with advanced colorectal cancer. We report a randomized trial that was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in collaboration with the Australasian Gastro-Intestinal Trials Group (AGITG).

METHODS

The study was designed by a protocol committee that included members of the NCIC CTG and the AGITG. The NCIC CTG collected, managed, and analyzed the data. Employees of Bristol-Myers Squibb and all the other authors reviewed the final manuscript and provided comments on it. NCIC CTG maintains full unrestricted rights to publication of the study data. Prepublication confidentiality of results was maintained by both the NCIC CTG and Bristol-Myers Squibb. The relevant institutional review boards approved the protocol, and all participants gave written informed consent.

Eligible patients had advanced colorectal cancer expressing EGFR that was detectable by immunohistochemical methods in a central reference laboratory. The patients either had been treated with a fluoropyrimidine (e.g., fluorouracil or capecitabine), irinotecan, and oxaliplatin with no response to treatment (as defined by unacceptable adverse events or progression of the tumor within 6 months of completion of treatment) or had contraindications to treatment with these drugs. The patients had disease that could be measured or otherwise evaluated; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate bone marrow, kidney, and liver function; and no serious concurrent illness. Patients were ineligible if they had received any agent that targets the EGFR pathway (e.g., cetuximab, erlotinib, gefitinib, or panitumumab) or treatment with a murine monoclonal antibody. Previous bevacizumab therapy was permitted but not required.

RANDOMIZATION

Eligible patients were stratified according to center and ECOG performance status (0 or 1 vs. 2) and randomly assigned between December 2003 and August 2005 at a 1:1 ratio to cetuximab plus best supportive care or best supportive care alone. Randomization was performed by the NCIC CTG central office with the use of a minimization method that dynamically balanced patients according to stratification factors.[15] The database was maintained by the NCIC CTG.

TREATMENTS

All patients received best supportive care, which was defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible. Because the patients had cancer that was refractory to all recommended chemotherapy, further chemotherapy or other antineoplastic therapy was not intended, although some patients did receive therapy after the completion of protocol procedures.

Cetuximab was given intravenously as an initial dose of 400 mg per square meter of body-surface area, administered over a period of 120 minutes, followed by a weekly maintenance infusion of 250 mg per square meter, administered over a period of 60 minutes. An antihistamine was given 30 to 60 minutes before each dose of cetuximab. Treatment was continued until death, in the absence of the occurrence of unacceptable adverse events, tumor progression, worsening symptoms of the cancer, or request by the patient, with or without the withdrawal of consent for continued follow-up.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Cetuximab plus Best Supportive Care (N=287)	Best Supportive Care Alone (N=285)
Age — yr		
Median	63.0	63.6
Range	28.6–88.1	28.7–85.9
Sex — no. (%)		
Female	101 (35.2)	103 (36.1)
Male	186 (64.8)	182 (63.9)
ECOG performance status — no. (%)		
0	72 (25.1)	64 (22.5)
1	148 (51.6)	154 (54.0)
2	67 (23.3)	67 (23.5)
Site of primary cancer — no. (%)		
Colon only	171 (59.6)	161 (56.5)
Rectum only	63 (22.0)	70 (24.6)
Colon and rectum	53 (18.5)	54 (18.9)
Any previous radiotherapy — no. (%)	103 (35.9)	99 (34.7)
Previous chemotherapy — no. (%)		
Adjuvant therapy	108 (37.6)	103 (36.1)
No. of regimens (including adjuvant)		
1 or 2	50 (17.4)	54 (18.9)
3	109 (38.0)	108 (37.9)
4	87 (30.3)	72 (25.3)
≥5	41 (14.3)	51 (17.9)
Thymidylate synthase inhibitor	287 (100)	285 (100)
Irinotecan	277 (96.5)	273 (95.8)
Oxaliplatin	281 (97.9)	278 (97.5)
Site of disease — no. (%)		
Liver	230 (80.1)	233 (81.8)
Lung	188 (65.5)	180 (63.2)
Lymph nodes	130 (45.3)	117 (41.1)
Peritoneal cavity (ascites)	45 (15.7)	41 (14.4)
No. of sites of disease — no. (%)		
1	40 (13.9)	53 (18.6)
2	84 (29.3)	69 (24.2)
3	84 (29.3)	89 (31.2)
≥4	79 (27.5)	74 (26.0)

* ECOG denotes Eastern Cooperative Oncology Group. Percentages may not total 100 because of rounding.

ASSESSMENTS

All patients were assessed every 4 weeks. Telephone monitoring was conducted until death for patients unable to attend the clinic. Chest radiographs and cross-sectional imaging were performed at baseline and every 8 weeks in both study groups until tumor progression occurred. Quality of life was assessed by the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) at baseline and at 4, 8, 16, and 24 weeks after randomization.[16,17]

STATISTICAL ANALYSIS

The primary end point of this study was overall survival, defined as the time from randomization until death from any cause. It was estimated a priori that 445 deaths would provide a statistical power of 90% and a two-sided alpha of 5% to detect an absolute increase of 9.6% in the 1-year overall survival from the predicted 1-year overall survival of 14.1% in the group assigned to supportive care alone (hazard ratio, 0.74). The final analysis was conducted after at least 445 patients were known to have died; March 6, 2006, was established as the data cutoff date.

The secondary end points were progression-free survival, defined as the time from randomization until the first objective observation of disease progression or death from any cause; response rates, defined according to the Modified Response Evaluation Criteria in Solid Tumors (RECIST); and quality of life, assessed by mean changes in scores of physical function and global health status at 8 and 16 weeks. The safety profile of cetuximab was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0.

All patients who underwent randomization were included in the efficacy analyses on the basis of the group to which they were assigned. Safety analysis was conducted on an on-treatment basis, contrasting patients who had at least one dose of cetuximab (including those who crossed over) with patients assigned to supportive care alone, and omitting patients who withdrew consent before any intervention. Time-to-event variables were summarized with the use of Kaplan–Meier plots. Primary comparisons of the treatment groups were made with the use of the stratified log-rank test adjusted for ECOG performance status at randomization. Hazard ratios with 95% confidence

intervals were calculated from stratified Cox regression models with treatment group as the single factor.[18] Quality-of-life scores for physical function and global health status were standardized to range from 0 to 100, with higher scores indicating better quality of life.[14] Deterioration in these quality-of-life scores was defined a priori as a decline of 10 points or more from baseline. Discrete variables were compared with the use of Fisher's exact test, and continuous and ordinal categorical variables with the use of the Wilcoxon test. An exploratory analysis of the effect of other potential prognostic factors specified a priori in the protocol was conducted by a multivariable Cox regression model stratified according to ECOG performance status at randomization. All P values were two-sided, and no adjustment was made for multiple comparisons. The final analysis was conducted by the NCIC CTG.

RESULTS

We randomly assigned 572 patients to treatment: 287 to cetuximab plus best supportive care and 285 to best supportive care alone. Four patients assigned to the cetuximab group never received the drug, and five patients assigned to receive supportive care alone subsequently received cetuximab off protocol. Six patients assigned to supportive care alone immediately withdrew their consent. Four patients (two in each group) were ineligible because of elevated bilirubin levels, other cancer, refusal to complete a quality-of-life assessment at baseline, or death on the date of randomization. All were included in the analyses. The two groups were similar with respect to baseline characteristics (Table 1). The median duration of follow-up was 14.6 months.

TREATMENT

The median duration of cetuximab treatment was 8.1 weeks (range, 1 to 60). Thirty-three patients (11.5%) had at least one dose reduction; rash, characteristically an acneiform papulopustular rash involving the face and trunk, was the most frequent reason (3.5%). One or more dose omissions occurred in 136 patients; intercurrent illness, rash, and patient request were the most common reasons. In 45 patients (15.7%), the infusion rate was decreased or infusion was interrupted at least once, most often because of a hypersensitivity reaction.

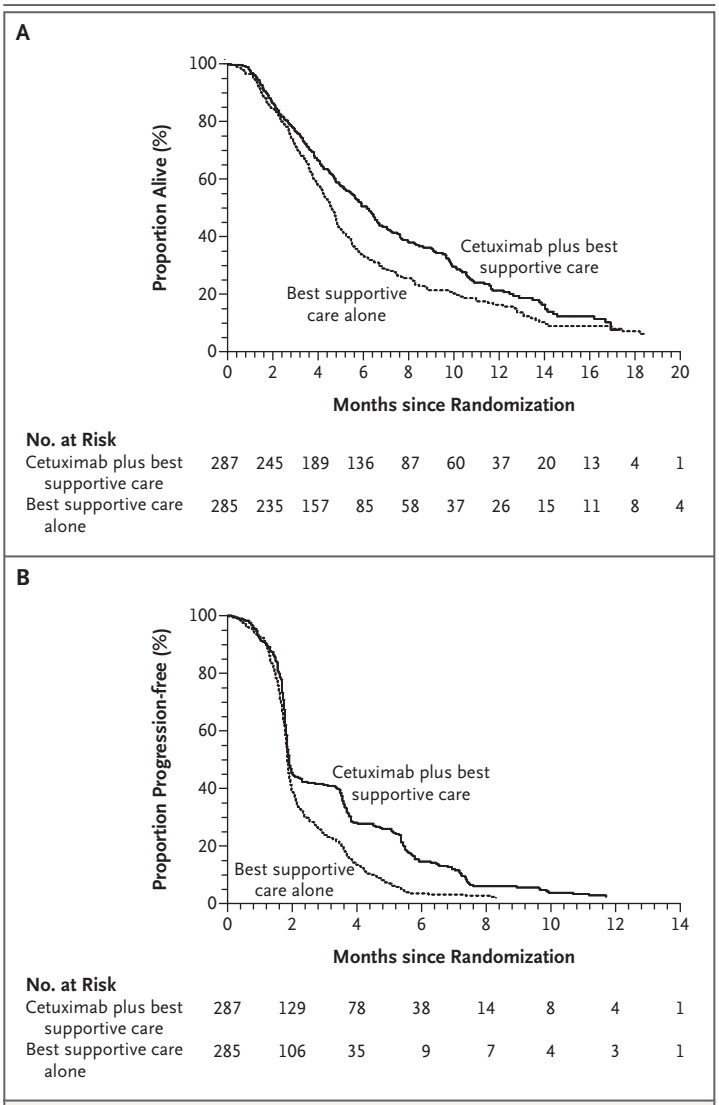


Figure 1. Kaplan–Meier Curves for Overall Survival (Panel A) and Progression-free Survival (Panel B).

The median dose intensity of cetuximab infusion after the initial dose was 247 mg per square meter per week; the relative dose intensity (the ratio of the dose administered to the planned dose) was 90% or higher in 75% of patients. At the time of data cutoff, 271 of the 283 patients had discontinued cetuximab treatment. Progressive disease and symptomatic progression were the principal reasons for cessation of treatment.

EFFICACY

Figure 1A shows overall survival in the two groups. A total of 456 deaths (222 in the cetuximab group

and 234 in the supportive-care group) had occurred by the date of analysis. All except 6 of these 456 patients died of colorectal cancer. The addition of cetuximab to supportive care resulted in longer overall survival than did supportive care alone (hazard ratio for death, 0.77; 95% confidence interval [CI], 0.64 to 0.92; P=0.005). The median survival was 6.1 months in the cetuximab group and 4.6 months in the supportive-care group. The proportions of patients surviving at 6 and 12 months were 50% and 21%, respectively, in the cetuximab group and 33% and 16%, respectively, in the supportive-care group. This difference remained statistically significant after adjustment for other protocol-specified potential prognostic factors with the use of a multivariable Cox regression model (hazard ratio, 0.79; 95% CI, 0.65 to 0.95; P=0.01). Factors other than treatment that were associated with survival in the multivariable analysis were sex; baseline levels of lactic dehydrogenase, alkaline phosphatase, and hemoglobin; and number of disease sites.

In a planned subgroup analysis, no significant differences in the relative benefit of cetuximab were seen across subgroups defined on the basis of ECOG performance status at baseline, age, or sex (Fig. 2). An unplanned landmark-type analysis that excluded all patients who died within 28 days after the start of the study demonstrated that the grade of rash in patients receiving cetuximab was strongly correlated with overall survival, with median survival of 2.6 months in patients with no rash, as compared with 4.8 months in patients with grade 1 rash and 8.4 months in patients with grade 2 rash (P<0.001) (Fig. 3). The median time to the onset of a rash in patients who received cetuximab was 10 days; in 90% of patients with a rash, the rash developed within 29 days.

Objective progression of the tumor was observed in 402 patients (224 in the cetuximab group and 178 in the supportive-care group), and 140 patients (49 in the cetuximab group and 91 in the supportive-care group) died without documented objective progression. Treatment with cetuximab resulted in a significant improvement in progression-free survival (hazard ratio for disease progression or death, 0.68; 95% CI, 0.57 to 0.80; P<0.001) (Fig. 1B). This difference remained statistically significant after adjustment for other protocol-specified potential prognostic factors (hazard ratio, 0.71; 95% CI, 0.59 to 0.85; P<0.001). Similar relative benefits of cetuximab in terms of progression-free survival were seen in subgroups defined on the basis of ECOG performance status at baseline, age, and sex. The estimated proportions of patients who were alive without documented objective progression of disease at 3 and 6 months were 41% and 15%, respectively, in the cetuximab group and 24% and 3%, respectively, in the supportive-care group.

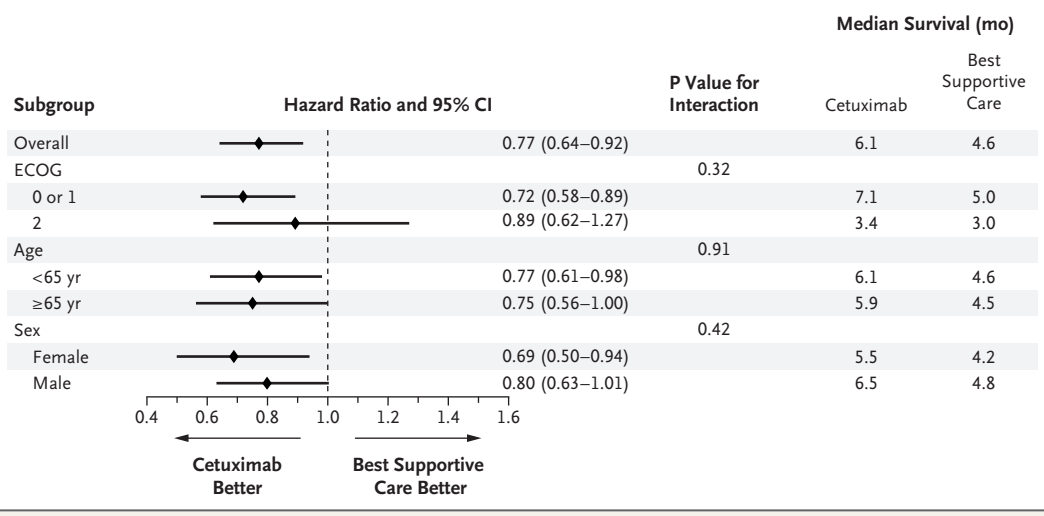


Figure 2. Forest Plot Demonstrating Hazard Ratios for Death According to Planned Subgroup Analysis.
The subgroup of race is not shown because of the insufficient number of nonwhite patients. ECOG denotes Eastern Cooperative Oncology Group.

Twenty-three patients (8.0%) in the cetuximab group and none in the supportive-care group had partial responses (P<0.001). Stable disease was observed in 90 patients in the cetuximab group (31.4%) and 31 patients in the supportive-care group (10.9%, P<0.001).

Compliance with the quality-of-life questionnaire was 94% at baseline in both groups, 81% at 8 weeks and 67% at 16 weeks in the cetuximab group, and 62% at 8 weeks and 43% at 16 weeks in the supportive-care group. As compared with supportive care alone, cetuximab treatment was associated with less deterioration in physical function at 8 weeks (mean change score, −3.9 vs. −8.6; P<0.05 by the Wilcoxon test) and 16 weeks (mean change score, −5.9 vs. −12.5; P=0.03). Cetuximab treatment was also associated with less deterioration in global health status at 8 weeks (mean change score, −0.5 vs. −7.1; P=0.008) and 16 weeks (mean change score, −3.6 vs. −15.2; P<0.001).

SAFETY

Adverse events of interest or with an incidence of at least 5% at grade 3 or higher, according to the NCI-CTC, version 2.0, are summarized in Table 2. There were no statistically significant differences between the cetuximab group and the supportive-care group in the incidence of grade 3 or higher adverse events, with the exception of rash (11.8% for cetuximab vs. 0.4% for supportive care, P<0.001), infection without neutropenia (12.8% vs. 5.5%, P=0.003), confusion (5.6% vs. 2.2%, P=0.05), and pain defined as "other" according to the NCI-CTC (14.9% vs. 7.3%, P=0.005). Hematologic adverse events were uncommon, and there were no significant differences between the groups in grade 3 or higher (according to the NCI-CTC) serum chemical values or other laboratory measurements, with the exception of hypomagnesemia, which was more common in the cetuximab group than in the group receiving supportive care alone (5.8% vs. 0.0%, P<0.001). Grade 3 or 4 infusion reactions (hypersensitivity) occurred in 4.5% of patients assigned to cetuximab.

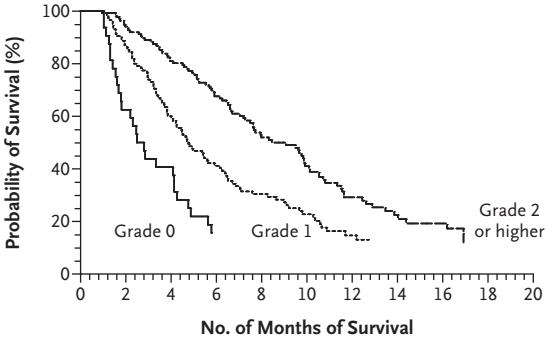
As compared with patients in the supportive-care group, patients in the cetuximab group had a higher incidence of rash of any grade (88.6% vs. 16.1%, P<0.001), hypomagnesemia of any grade (53.3% vs. 15.1%, P<0.001), and infusion reactions of any grade (20.5% vs. 0.0%, P<0.001).

Fifty-nine patients died within 30 days after the last date of the cetuximab infusion. All died of colorectal cancer except one patient who had a pulmonary embolus. Eleven patients had adverse events leading to discontinuation of cetuximab, most frequently because of an infusion reaction.

DISCUSSION

This study showed that cetuximab can improve overall survival in patients with colorectal cancer in whom other treatments have failed. Cetuximab alone — not in combination with other agents — improved survival. This trial was not blinded, which raises the possibility of bias in the assessment of progression-free survival but not overall survival. The hazard ratios for death (0.77) and disease progression or death (0.68) suggest minimal bias.

The interpretation of quality-of-life data is complicated by differences in compliance rates between the two groups; rapid disease progression in the group assigned to supportive care alone is likely to have resulted in a lower compliance rate. The tumor response rates were similar to rates reported in previous studies of cetuximab and



No. at Risk

Grade 0	32	20	13	5	3	3	3	2	1	0	0
Grade 1	115	100	69	43	30	18	9	4	2	1	0
Grade 2 or higher	136	128	110	89	55	40	25	14	10	3	1

Figure 3. Overall Survival According to the Worst Grade of Rash in the Cetuximab Group.

Patients surviving for less than 1 month were excluded from this analysis to reduce exposure-opportunity bias. The hazard ratios for death were as follows: grade 2 or higher versus grade 0 rash, 0.33 (95% CI, 0.22 to 0.50; P<0.001); grade 1 versus grade 0 rash, 0.61 (95% CI, 0.40 to 0.93; P<0.02); and grade 2 or higher versus grade 1 rash, 0.54 (95% CI, 0.41 to 0.72; P<0.001). The median survival times for patients surviving for at least 28 days with a rash of grade 0 (32 patients) was 2.6 months, with a rash of grade 1 (115 patients) was 4.8 months, and with a rash of grade 2 or higher (136 patients) was 8.4 months.

Table 2. Adverse Events.

Event	Cetuximab plus Best Supportive Care (N=288)				Best Supportive Care Alone (N=274)				P Value
	number (percent)								
Grade 3 or higher with an incidence of ≥5%*									
Any adverse event	226 (78.5)				162 (59.1)				<0.001
Edema	15 (5.2)				16 (5.8)				0.85
Fatigue	95 (33.0)				71 (25.9)				0.09
Anorexia	24 (8.3)				16 (5.8)				0.32
Constipation	10 (3.5)				13 (4.7)				0.53
Nausea	16 (5.6)				15 (5.5)				1.00
Vomiting	16 (5.6)				15 (5.5)				1.00
Non-neutropenic infection	37 (12.8)				15 (5.5)				0.003
Confusion	16 (5.6)				6 (2.2)				0.05
Abdominal pain	38 (13.2)				43 (15.7)				0.40
Other pain†	43 (14.9)				20 (7.3)				0.005
Dyspnea	47 (16.3)				34 (12.4)				0.23
Rash	34 (11.8)				1 (0.4)				<0.001
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	
	number (percent)								
Other adverse events‡									
Infusion reactions	30 (10.4)	16 (5.6)	8 (2.8)	5 (1.7)	0	0	0	0	<0.001
Rash	114 (39.6)	107 (37.2)	34 (11.8)	0	32 (11.7)	11 (4.0)	1 (0.4)	0	<0.001
Hypomagnesemia§	95 (36.7)	28 (10.8)	7 (2.7)	8 (3.1)	29 (14.6)	1 (0.5)	0	0	<0.001

* Grades were determined according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0.
† This category excludes arthralgia; myalgia; earache; headache; and abdominal, bone, chest, hepatic, neuropathic, pelvic, pleuritic, rectal, perirectal, and tumor pain.
‡ The P values, calculated with the use of Fisher's exact test, are for the difference in the incidence of adverse events between the two treatment groups.
§ The results for hypomagnesemia are based on 259 patients in the cetuximab group and 198 patients in the supportive-care group.

other anti-EGFR antibodies.[12,13] Our results suggest that stabilization of disease and response to the treatment contribute to the prolongation of survival but that tumor response alone may not be a useful surrogate outcome.

Initial studies of the treatment of colorectal cancer with cetuximab were performed in patients whose tumors had immunohistochemically detectable EGFR, but there is evidence that the intensity of staining of the tumor section for EGFR correlates poorly with the response to cetuximab. Moreover, responses have been reported in patients with tumors without immunohistochemically detectable EGFR.[19,20] Although it is unknown whether the improvements in survival can be extrapolated to the patients with EGFR-negative tumors, immunohistochemically detectable EGFR is no longer considered a clinically useful biomarker.[21]

This study further validates the use of EGFR as a biologic target in colorectal cancer; however, not all EGFR inhibitors are equally efficacious against this disease. The EGFR tyrosine kinase inhibitors erlotinib and gefitinib have less activity against EGFR than do monoclonal antibodies.[22,23] A study that compared the human anti-EGFR monoclonal antibody panitumumab with supportive care found a decrease in the time to progression of the disease but no improvement in overall survival with panitumumab.[24]

Cetuximab has the ability to reverse resistance

to irinotecan.[13] Studies in which cetuximab was combined with irinotecan in the treatment of colorectal cancer found improvements in response rates and progression-free survival but not in overall survival.[13,25-27] The uncoupling of overall survival benefits from progression-free survival benefits in these combination studies is probably due in part to intentional or unintentional crossover, whereby patients assigned initially to a group without cetuximab eventually received cetuximab after progression. If the absolute survival benefit of cetuximab is similar whether it is given earlier or later in the course of treatment for advanced colorectal cancer, no survival difference will be seen in studies with substantial crossover. In contrast to the findings of these combination studies, only 7.0% of patients in our trial who were receiving supportive care alone subsequently received cetuximab, and only 27.5% of patients in the cetuximab group, versus 23.2% of patients in the supportive-care group, received any anticancer treatment after progression of the disease. The collective data suggest that cetuximab can benefit patients with advanced colorectal cancer, whether their disease is resistant or sensitive to chemotherapy.

Tumor progression had occurred in more than 50% of patients in both groups of our study by the time of the first computed tomographic scan, and the median progression-free survival did not differ between the groups (1.8 months in the supportive-care group vs. 1.9 months in the cetuximab group). However, the hazard ratio of 0.68 for disease progression or death is reflected in a clear separation of the curves after the median.

The disease was stable or responded to therapy in only 39.4% of the patients in the cetuximab group, a result indicating a need for predictive biomarkers to identify patients who could benefit from such treatment. Rash related to EGFR inhibition, which is due to alteration of the mediation of epidermal basal keratinocytes by EGFR, is one such potential biomarker. Analysis of the incidence of the rash suggests that it may be a predictive marker, but this point has not been validated.

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APPENDIX

In addition to the authors, the following committee members, site investigators, data managers, and key trial staff participated in the CO.17 study from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG). **NCIC CTG investigators in Canada:** Dr. H. Bliss Murphy Cancer Centre, St. John's, NB — J. Siddiqui; QEII Health Sciences Center, Halifax, NS — B. Colwell; Atlantic Health Sciences Corporation, St. John's, NB — M. Burnell; Moncton Hospital, Moncton, NB — S. Rubin; Hôpital du Sacré-Coeur de Montréal, Montreal — R. Whittom; Centre Hospitalier de l'Université de Montréal–Hôpital Notre-Dame, Montreal — D. Charpentier; Hôpital Charles LeMoyne, Greenfield Park, QC — B. Samson; Cancer Centre of Southeastern Ontario, Kingston — A. Tomiak; Quinte Healthcare Corporation, Belleville, ON — R. Levesque; Niagara Health System, Ontario — B. Findlay; Toronto East General Hospital, Toronto — J. Meharchand; St. Joseph's Health Centre, Toronto — J. Blondal; Mount Sinai Hospital, Toronto — R. Burkes; St. Michael's Hospital, Toronto — R. Haq; Grand River Regional Cancer Centre, Kitchener, ON — G. Knight; London Regional Cancer Program, Ontario — I. Kerr; Windsor Regional Cancer Centre, Ontario — J. Mathews; Thunder Bay Regional Health Science Centre, North Bay, ON — D. Dueck; Allan Blair Cancer Centre, Regina, SK — H. Chalchal; Saskatoon Cancer Centre, Saskatoon, SK — S. Yadav; Cross Cancer Institute, Edmonton, AB — S. Koski; BC Cancer Agency–Vancouver Cancer Centre, Vancouver, BC — H. Kennecke; BC Cancer Agency–Cancer Centre for the Southern Interior, Kelowna, BC — M. Taylor; BC Cancer Agency–Vancouver Island Cancer Centre, Victoria, BC — H. Anderson; BC Cancer Agency–Fraser Valley Cancer Centre, Surrey, BC — U. Lee. **NCIC CTG central office staff, Kingston, ON:** S. Robitaille, N. Magoski, S. Hunt, A. Lewis, D. Nomikos, J. Ottaway, A. Hung, A. Sargeant, V. Classen, J. Baran, L. Pho, A. Garrah, L. Zhu. **Australasian Gastro-Intestinal Trials Group (AGITG) investigators in Australia:** Newcastle Mater Misericordiae Hospital, New South Wales — S. Ackland; Port Macquarie Base Hospital, New South Wales — S. Begbie; St. Vincent's Hospital, Victoria — I. Burns; Launceston General Hospital, Tasmania — I. Byard; Fremantle Hospital, Western Australia — P. Claringbold; Royal Melbourne Hospital, Victoria — P. Gibbs; Prince of Wales Hospital, New South Wales — D. Goldstein; Peter MacCallum Cancer Institute, Victoria — M. Jefford; St. George Hospital, New South Wales — M. Links; Royal Hobart Hospital, Tasmania — R. Lowenthal; Brisbane Adult Mater, Queensland — P. Mainwaring; Royal North Shore Hospital, New South Wales — N. Pavlakis; St. John of God Subiaco, Western Australia — D. Ransom; Nepean Hospital, New South Wales — J. Shannon; Cabrini Hospital, Victoria, and Alfred Hospital, Victoria — J. Shapiro; Monash Medical Centre, Victoria — A. Strickland; Royal Perth Hospital, Western Australia — J. Trotter; Border Medical Oncology, Victoria — C. Underhill; Royal Brisbane Hospital, Queensland — D. Wyld; Canberra Hospital, Australian Capital Territory — D. Yip. **AGITG investigators in New Zealand:** Palmerston North Hospital, Palmerston North — R. Isaacs; Christchurch Hospital, Christchurch — M. Jeffrey. **AGITG investigator in Singapore:** National Cancer Centre Singapore — K.F. Foo. **Australian National Health and Medical Research Council (NHMRC) Clinical Trials Centre (AGITG Coordinating Centre) staff:** B. Cakir, A. Pearce, C. Aiken, J. Simard-Lebrun, J. Shoulder, F. Howard. **Bristol-Myers Squibb:** J. Dechamplain, N. Gustafson.

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