

ORIGINAL ARTICLE

Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer

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ABSTRACT

BACKGROUND

The epidermal growth factor receptor (EGFR), which participates in signaling pathways that are deregulated in cancer cells, commonly appears on colorectal-cancer cells. Cetuximab is a monoclonal antibody that specifically blocks the EGFR. We compared the efficacy of cetuximab in combination with irinotecan with that of cetuximab alone in metastatic colorectal cancer that was refractory to treatment with irinotecan.

METHODS

We randomly assigned 329 patients whose disease had progressed during or within three months after treatment with an irinotecan-based regimen to receive either cetuximab and irinotecan (at the same dose and schedule as in a prestudy regimen [218 patients]) or cetuximab monotherapy (111 patients). In cases of disease progression, the addition of irinotecan to cetuximab monotherapy was permitted. The patients were evaluated radiologically for tumor response and were also evaluated for the time to tumor progression, survival, and side effects of treatment.

RESULTS

The rate of response in the combination-therapy group was significantly higher than that in the monotherapy group (22.9 percent [95 percent confidence interval, 17.5 to 29.1 percent] vs. 10.8 percent [95 percent confidence interval, 5.7 to 18.1 percent], $P=0.007$). The median time to progression was significantly greater in the combination-therapy group (4.1 vs. 1.5 months, $P<0.001$ by the log-rank test). The median survival time was 8.6 months in the combination-therapy group and 6.9 months in the monotherapy group ($P=0.48$). Toxic effects were more frequent in the combination-therapy group, but their severity and incidence were similar to those that would be expected with irinotecan alone.

CONCLUSIONS

Cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer.

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IN THE PAST DECADE, THE MEDIAN DURATION of survival among patients with advanced colorectal cancer has increased from 12 months to about 18 to 21 months, mainly owing to the introduction of irinotecan and oxaliplatin. Irinotecan (a semisynthetic camptothecin, which inhibits topoisomerase I) and oxaliplatin (a third-generation platinum compound) are widely used in combination with fluorouracil and leucovorin as first-line treatment for advanced colorectal cancer.¹⁻⁵ Irinotecan alone can also confer benefit in patients with colorectal cancer that is refractory to treatment with fluorouracil,^{6,7} and oxaliplatin can be effective in patients with disease that is refractory to irinotecan treatment.⁸

Epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors, is relevant in colorectal cancer because expression or up-regulation of the *EGFR* gene occurs in 60 to 80 percent of cases.⁹⁻¹¹ Moreover, expression of the gene is associated with poor survival.^{12,13} When inactive, EGFR is a monomer, but when bound by epidermal growth factor or transforming growth factor α (TGF- α), it forms homodimers or heterodimers with another member of the ErbB family of receptors. Dimerization activates the intracellular tyrosine kinase region of EGFR, resulting in autophosphorylation and initiating a cascade of intracellular events.¹⁴ The EGFR signaling pathway regulates cell differentiation, proliferation, migration, angiogenesis, and apoptosis, all of which become deregulated in cancer cells.¹⁵ Cetuximab (Erbix, Merck and Imclone Systems) is a chimeric IgG1 monoclonal antibody that binds to EGFR with high specificity and with a higher affinity than either epidermal growth factor or TGF- α , thus blocking ligand-induced phosphorylation of EGFR. In addition, cetuximab enhances the effects of irinotecan¹⁶ and radiotherapy in experimental systems.

A phase 2 study of weekly cetuximab and irinotecan in 121 patients who had colorectal cancer that was refractory to fluorouracil and irinotecan found a 17 percent response rate.¹⁷ In a study of 57 patients with EGFR-positive colorectal cancer that was refractory to both fluorouracil and irinotecan, 8.8 percent of the patients had a partial response to cetuximab monotherapy, and 36.8 percent had stable disease.¹⁸

In the present trial, we compared the combination of cetuximab and irinotecan with cetuximab monotherapy in patients with EGFR-expressing irinotecan-refractory colorectal cancer.

METHODS

PATIENTS

We considered patients eligible if they were more than 18 years of age and had stage IV, histologically confirmed colorectal adenocarcinoma. Other criteria for eligibility were a Karnofsky performance-status score of 60 or more, adequate hematologic function (hemoglobin, at least 9 g per deciliter [5.6 mmol per liter]; neutrophil count, at least 1500 per cubic millimeter; and platelet count, at least 100,000 per cubic millimeter), renal function (serum creatinine, less than 1.5 times the upper limit of normal), and liver function (bilirubin, not more than 1.5 times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase, not more than 5 times the upper limit of normal).

To be eligible, patients must also have received one of several qualifying, prestudy irinotecan regimens for at least six weeks and must have had documented progression of disease during receipt of this regimen or within three months thereafter. These regimens were irinotecan at a dose of 125 mg per square meter of body-surface area given weekly for four consecutive weeks, followed by two weeks' rest, as a single agent or in combination with fluorouracil and leucovorin; irinotecan at a dose of 180 mg per square meter given every two weeks in combination with fluorouracil and leucovorin; and irinotecan at a dose of 350 mg per square meter given every three weeks as a single agent. Disease progression was documented by computed tomography (CT) or magnetic resonance imaging (MR); new lung lesions could be documented by chest radiography. At least one unidimensionally measurable lesion was required, as was immunohistochemical evidence of EGFR expression, either in the primary tumor or in at least one metastatic lesion.

All the patients signed a consent form. The study was approved by the institutional ethics committees of all the participating centers.

STUDY DESIGN AND TREATMENT

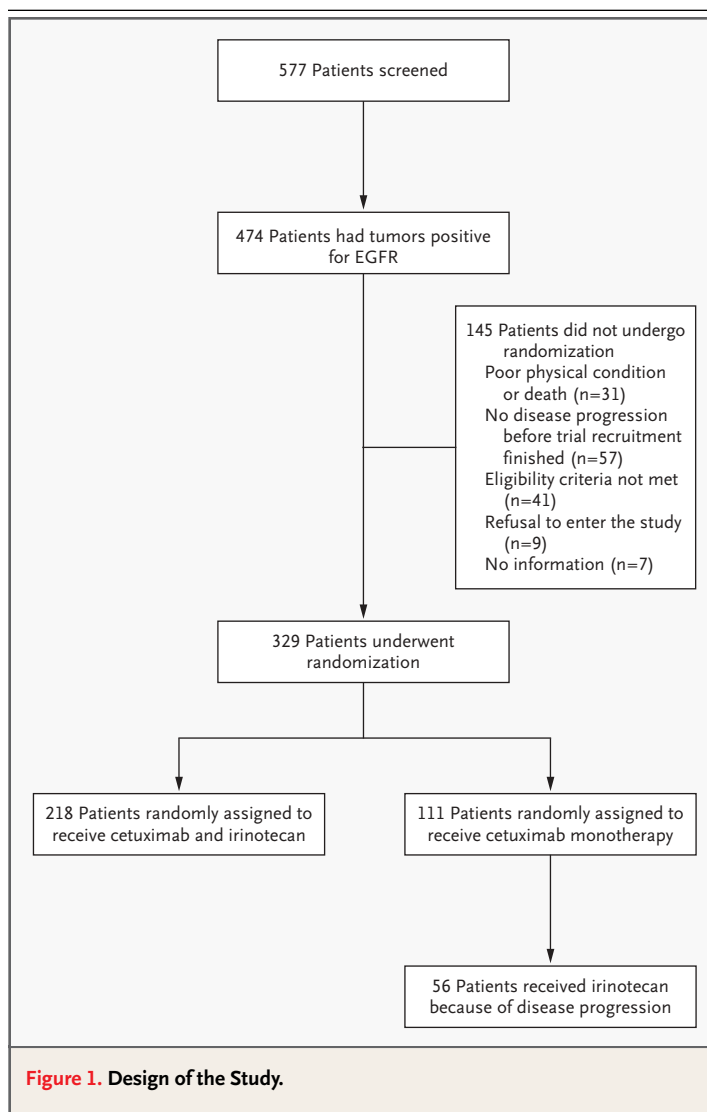
This open-label, randomized trial was conducted in 56 centers in 11 European countries (the participating investigators are listed in the Appendix). Before randomization, the EGFR status of the tumor was determined at a central location in Germany by immunohistochemical analysis of a paraffin-embedded tumor specimen with the use of an EGFR diagnostic kit (Dako Cytomation). Random assignment of the eligible patients to either cetuximab in

combination with irinotecan or cetuximab alone in a ratio of 2:1 was carried out centrally by an independent randomization service. Randomization was performed by a minimization technique, with stratification according to Karnofsky performance status, previous treatment with or without prior use of oxaliplatin, and treatment center.

Cetuximab was given at an initial dose of 400 mg per square meter, followed by weekly infusions of 250 mg per square meter. A histamine-receptor antagonist was given as premedication before at least the first infusion. Patients assigned to the combination-therapy group also received irinotecan at the same dose as that given during their most recent prestudy therapy. All the patients were to be treated until disease progression or unacceptable toxic effects occurred. In the case of disease progression, patients assigned to the monotherapy group could continue to receive cetuximab, and irinotecan could be added at the same dose as that given during their most recent prestudy therapy.

Tumor response was evaluated every 6 weeks for the first 24 weeks and thereafter every 3 months with the use of consistent imaging techniques (CT or MRI). Assessment was performed by the investigators, who used the Response Evaluation Criteria in Solid Tumors (RECIST)¹⁹ and by an independent review committee consisting of three radiologists and one oncologist who used modified World Health Organization (WHO) criteria.²⁰

In brief, on the basis of the WHO criteria, a complete response was defined as the complete disappearance of all measurable lesions, without the appearance of any new lesions. A partial response was defined as a reduction in bidimensionally measurable lesions by at least 50 percent of the sum of the products of their largest perpendicular diameters and an absence of progression in other lesions, without the appearance of any new lesions. Stable disease was defined as a reduction in tumor volume of less than 50 percent or an increase in the volume of one or more measurable lesions of less than 25 percent, without the appearance of any new lesions. Progressive disease was defined as an increase in the size of at least one bidimensionally measurable lesion by at least 25 percent and the appearance of new lesions. The change from use of the RECIST criteria to the WHO criteria followed a Food and Drug Administration advisory that indicated that use of the WHO criteria would facilitate an independent review of three major studies to be submitted for approval of cetuximab in the United States and Europe.



The independent review committee, which was blinded to the treatment assignment, assessed disease progression during the irinotecan regimen given before enrollment in the study and the response and time to progression during the study. To do so, the committee used the WHO criteria and compared CT scans or MRI images obtained before enrollment and during the study. Toxic effects were assessed according to the National Cancer Institute Common Toxicity Criteria, version 2. Modifications of the dose of cetuximab were made only in cases of toxic effects to the skin, and modifications in the dose of irinotecan were made in cases of hematologic or nonhematologic toxic effects.

The investigators and representatives from Merck designed the study. The data were collected

Table 1. Baseline Characteristics of the Patients.

Characteristic	Cetuximab plus Irinotecan (N=218)	Cetuximab Monotherapy (N=111)	Total (N=329)
Age — yr			
Median	59	58	59
Range	26–82	39–84	26–84
Sex — no. (%)			
Male	143 (65.6)	63 (56.8)	206 (62.6)
Female	75 (34.4)	48 (43.2)	123 (37.4)
Race — no. (%)			
White	214 (98.2)	109 (98.2)	323 (98.2)
Black	2 (0.9)	0	2 (0.6)
Asian	2 (0.9)	2 (1.8)	4 (1.2)
Karnofsky performance-status score — no. (%)			
<80	25 (11.5)	15 (13.5)	40 (12.2)
80–100	193 (88.5)	96 (86.5)	289 (87.8)
Previous adjuvant therapy — no. (%)	59 (27.1)	37 (33.3)	96 (29.2)
No. of previous cancer treatments — no. (%)			
One	41 (18.8)	27 (24.3)	68 (20.7)
Two	79 (36.2)	41 (36.9)	120 (36.5)
More than two	98 (45.0)	43 (38.7)	141 (42.9)
Prestudy irinotecan treatment — no. (%)			
125 mg/m ² /wk for 4 wk followed by 2-wk rest	33 (15.1)	20 (18.0)	53 (16.1)
180 mg/m ² every 2 wk	124 (56.9)	54 (48.6)	178 (54.1)
350 mg/m ² every 3 wk	57 (26.1)	31 (27.9)	88 (26.7)
Other regimens	4 (1.8)	6 (5.4)	10 (3.0)
Prior oxaliplatin treatment — no. (%)	135 (61.9)	71 (64.0)	206 (62.6)
Percentage of cells positive for epidermal growth factor receptor — no. (%)			
0 to <10	94 (43.1)	41 (36.9)	135 (41.0)
10 to <20	23 (10.6)	22 (19.8)	45 (13.7)
20 to <40	39 (17.9)	16 (14.4)	55 (16.7)
≥40	62 (28.4)	32 (28.8)	94 (28.6)

and analyzed by medical and statistical representatives from Merck, who worked in conjunction with the investigators. All the investigators had access to the primary data and participated in writing the manuscript. All the participating institutions received grant support from Merck for conducting the study.

STATISTICAL ANALYSIS

The primary end point was the rate of confirmed radiologic tumor response, as assessed by the independent review committee, in the intention-to-treat population. Differences in response rates between the two groups were evaluated by means of a two-sided Fisher's exact test. A P value of less than 0.05 was considered to indicate statistical signifi-

cance. Secondary end points included the time to progression, the duration of response, overall survival time, and the incidence of adverse effects. The time to progression was calculated as the period from the date of randomization to the first observation of disease progression or to death from any cause within 60 days after randomization or the most recent tumor assessment. The overall survival time was calculated as the period from the date of randomization until death from any cause or until the date of the last follow-up, at which point data were censored. Both the time to progression and overall survival time were estimated by the Kaplan–Meier method²¹ and compared between the two groups with use of the log-rank test.²² Stratified permutation tests were carried out to explore the association between tumor response and rash and between tumor response and EGFR expression.

The planned sample size for the study was based on power calculations related to the estimation of the confidence interval expected for the combination-therapy group. Anticipating a response rate of 19 percent in this group, we determined that 150 patients would be sufficient to exceed a clinically relevant nominal response rate of 10 percent, with 85 percent power. A response rate of 5 percent in the cetuximab-monotherapy group was expected. Given this expectation, a 2:1 randomization ratio was considered appropriate and ethically justified. Therefore the study was originally set up to assign 225 patients randomly to one of the two treatment groups. This sample size would also allow detection of a statistically significant difference in terms of response rates between the two groups, with a power of about 80 percent at a significance level of 0.05 by means of a two-sided Fisher's exact test. However, after the study had commenced and the majority of patients had been enrolled, the Swedish Medical Products Agency advised that patients whose disease had progressed at the end of irinotecan treatment or progressed within one month thereafter would be considered to have disease that was strictly refractory to irinotecan. Therefore, the sample size was increased to a total of 300 patients to ensure that the study objectives could be met for this subgroup of patients.

Predefined subgroup analyses included analyses of the patients whose disease progressed during or within one month after the end of the prestudy irinotecan treatment (as described above) and of patients who had received previous oxaliplatin treatment.

The cutoff point for survival data was January 2003; for safety data, it was November 2002. All analyses were performed using SAS software (version 8.2).

RESULTS

Between July 2001 and May 2002, 577 patients were screened; 474 of them (82.1 percent) had EGFR-positive tumors. Of these 474 patients, 329 were randomly assigned either to combination treatment with cetuximab and irinotecan (218 patients) or to cetuximab monotherapy (111 patients). Figure 1 shows the design of the trial. Major protocol deviations were reported in three patients. One patient in each group had a tumor with no evidence of EGFR expression, and one patient in the monotherapy group had no evidence of metastatic colorectal cancer at the time of enrollment. There were no major imbalances between the two groups in terms of baseline characteristics (Table 1). Nearly 80 percent of the patients who underwent randomization had received two or more previous regimens of treatment for cancer. All the patients had received irinotecan, and 206 (62.6 percent) had received oxaliplatin.

The overall response rate (the rate of complete response plus the rate of partial response) in the intention-to-treat population was 22.9 percent (95 percent confidence interval, 17.5 to 29.1 percent) in the combination-therapy group and 10.8 percent (95 percent confidence interval, 5.7 to 18.1 percent) in the monotherapy group ($P=0.007$) (Table 2). The median duration of response was 5.7 months in the combination-therapy group and 4.2 months in the monotherapy group. Disease control (complete response plus partial response plus stable disease) was achieved in 55.5 percent of patients receiving combination treatment and in 32.4 percent of patients treated with cetuximab alone ($P<0.001$). When the more stringent definition for irinotecan resistance (progression during or within one month after irinotecan therapy) was applied, the response rates were 25.2 percent (95 percent confidence interval, 18.1 to 33.4 percent) and 14.1 percent (95 percent confidence interval, 7.0 to 24.4 percent) in the combination-therapy and monotherapy groups, respectively ($P=0.07$), although the number of patients in this comparison (206) was small.

Of special interest is the finding that cetuximab-based therapy was similarly effective in patients who had previously received oxaliplatin in addition to

Table 2. Rates of Radiologic Response.*

Subgroup and Variable	Cetuximab plus Irinotecan		P Value
	Cetuximab plus Irinotecan	Cetuximab	
Intention-to-treat population			
No. of patients	218	111	
Response — no. (%)			
Complete response	0	0	
Partial response	50 (22.9)	12 (10.8)	
Stable disease	71 (32.6)	24 (21.6)	
Progressive disease	68 (31.2)	59 (53.2)	
Could not be evaluated	29 (13.3)	16 (14.4)	
Overall response†	50 (22.9 [17.5–29.1])	12 (10.8 [5.7–18.1])	0.007
Disease control‡	121 (55.5 [48.6–62.2])	36 (32.4 [23.9–42.0])	<0.001
Subgroup with progression during or within 4 wk after prestudy irinotecan			
No. of patients	135	71	
Response — no. (%)	34 (25.2 [18.1–33.4])	10 (14.1 [7.0–24.4])	0.07
Subgroup with prior oxaliplatin therapy			
No. of patients	135	71	
Response — no. (%)	30 (22.2 [15.5–30.2])	6 (8.5 [3.2–17.5])	0.01

* Values in brackets are 95 percent confidence intervals.

† The overall response rate is the sum of the rate of complete response and the rate of partial response.

‡ The rate of disease control is the sum of the rates of complete response, partial response, and stable disease.

irinotecan before entering the study. In these multiply pretreated patients, the response rate was 22.2 percent in the combination-therapy group and 8.5 percent in the monotherapy group ($P=0.01$). Statistical regression modeling revealed that the differences in response rates between the two treatment groups were maintained after adjustment for age, sex, performance status, and number of prior treatment regimens (data not shown).

The degree of EGFR expression, either as the percentage of EGFR-positive tumor cells or as the maximal staining intensity per cell, did not correlate significantly with the clinical response rate ($P=0.87$ and $P=0.64$, respectively) (Table 3). However, the response rates in patients with skin reactions after cetuximab treatment were higher than those in patients without skin reactions (25.8 percent vs. 6.3 percent in the combination-therapy group [$P=0.005$] and 13.0 percent vs. 0 percent in the monotherapy group).

Table 3. Influence of Epidermal Growth Factor Receptor Expression and Rash on Rates of Response.*

Variable	Cetuximab plus Irinotecan (N=218)	Cetuximab Monotherapy (N=111)	P Value for Trend
	<i>no./total no. (%)</i>		
Percentage of EGFR-expressing cells			0.87
≤10	25/109 (22.9)	4/56 (7.1)	
>10 to ≤20	4/20 (20.0)	5/16 (31.3)	
>20 to ≤35	6/27 (22.2)	0/7 (0)	
>35	15/62 (24.2)	3/32 (9.4)	
EGFR staining intensity			0.64
Faint	11/53 (20.8)	1/21 (4.8)	
Weak or moderate	22/89 (24.7)	7/55 (12.7)	
Strong	17/75 (22.7)	4/34 (11.8)	
Acne-like rash			
None vs. any			0.18
None	8/48 (16.7)	2/28 (7.1)	
Any	42/170 (24.7)	10/83 (12.0)	
None vs. grade 1 or 2 vs. grade 3 or 4			0.001
None	8/48 (16.7)	2/28 (7.1)	
Grade 1 or 2	29/148 (19.6)	9/79 (11.4)	
Grade 3 or 4	13/22 (59.1)	1/4 (25.0)	
Skin reaction			
None vs. any			0.005
None	2/32 (6.3)	0/19 (0)	
Any	48/186 (25.8)	12/92 (13.0)	
None vs. grade 1 or 2 vs. grade 3 or 4			<0.001
None	2/32 (6.3)	0/19 (0)	
Grade 1 or 2	32/157 (20.4)	10/86 (11.6)	
Grade 3 or 4	16/29 (55.2)	2/6 (33.3)	

* EGFR denotes epidermal growth factor receptor.

In the intention-to-treat analysis, the median time to progression of disease was 4.1 months in the combination-therapy group and 1.5 months in the monotherapy group. The hazard ratio for disease progression in the combination-therapy group was 0.54 (95 percent confidence interval, 0.42 to 0.71), indicating a 46 percent reduction in the risk of progression with combination therapy as compared with monotherapy ($P < 0.001$ by the log-rank test) (Fig. 2). In the combination-therapy group, the percentages of patients remaining free of progression at three and six months were 54 percent (95 percent confidence interval, 47 to 61 percent) and 30 percent (95 percent confidence interval, 23 to 37 percent), respectively. In the monotherapy group, the percentages of patients remaining free of progression at three and six months were 28 percent (95 percent confidence interval, 19 to 37 percent)

and 8 percent (95 percent confidence interval, 1 to 14 percent), respectively. The times to progression were similar among patients whose disease progressed during or within one month after prestudy irinotecan therapy and among those who had previously received oxaliplatin.

By January 2003, 215 of the 329 patients in the intention-to-treat analysis (65.3 percent) had died (140 in the combination-therapy group and 75 in the monotherapy group). The median overall survival time was 8.6 months in the combination-therapy group and 6.9 months in the monotherapy group. The hazard ratio for death with combination therapy, as compared with monotherapy, was 0.91 (95 percent confidence interval, 0.68 to 1.21), and there was no statistically significant difference between the two groups ($P = 0.48$ by the log-rank test) (Fig. 3). In the combination-therapy group, the overall survival rates at 6 and 12 months were 66 percent (95 percent confidence interval, 60 to 72 percent) and 29 percent (95 percent confidence interval, 22 to 37 percent), respectively. In the monotherapy group, the overall survival rates at 6 and 12 months were 58 percent (95 percent confidence interval, 49 to 67 percent) and 32 percent (95 percent confidence interval, 23 to 41 percent), respectively. The median survival times among patients with skin reactions and those without skin reactions were 9.1 and 3.0 months, respectively, in the combination-therapy group and 8.1 and 2.5 months, respectively, in the monotherapy group.

Fifty-six patients in the monotherapy group received additional irinotecan after disease progression was recognized. Two of these 56 patients (3.6 percent) had a partial response, and an additional 20 (35.7 percent) had stable disease after crossing over. The median time to progression among the patients who crossed over to receive additional irinotecan was 1.4 months. These results may in part explain the absence of a significant difference in overall survival between the two groups.

All the patients received at least one infusion of cetuximab. The median number of cetuximab infusions was 18 in the combination-therapy group and 7 in the monotherapy group. Table 4 summarizes the most frequently observed grade 3 or 4 adverse events related to treatment. Four patients who were randomly assigned to the combination-therapy group did not receive irinotecan and therefore were evaluated for safety as part of the monotherapy group, and two patients who were randomly assigned to the combination-therapy group did

not receive any study medication. In 4 of the 329 enrolled patients (1.2 percent), severe anaphylactic reactions to cetuximab developed, and the treatment was discontinued. There were no treatment-related deaths. Acne-like rash occurred in about 80 percent of the patients in each group, but grade 3 or 4 toxic effects on the skin were observed in only 9.4 percent and 5.2 percent of the combination-therapy and monotherapy groups, respectively. In 225 of the 253 patients in whom any form of acne-like rash developed (88.9 percent), the rash appeared within the first three weeks after the start of cetuximab treatment. Diarrhea and neutropenia were more frequent among the patients receiving irinotecan in combination with cetuximab than they were among those receiving cetuximab monotherapy, but the frequency of each was in the range that would be expected for irinotecan alone.

DISCUSSION

In this randomized trial, cetuximab alone or in combination with irinotecan had clinical activity in irinotecan-refractory colorectal cancer, confirming the results of phase 2 studies.^{17,18} The combination-therapy group had a significantly higher response rate and a significantly longer time to progression than the monotherapy group, suggesting that the combination of irinotecan and cetuximab should be preferred for patients with irinotecan-refractory cancer. Moreover, the number of previous treatment regimens and previous use or nonuse of oxaliplatin did not affect the efficacy of the cetuximab-and-irinotecan combination. Cetuximab monotherapy also had activity and only mild toxic effects and thus may be an option for patients who are not considered candidates for further treatment with irinotecan-based chemotherapy or who choose not to receive such treatment.

The effectiveness of the combination of irinotecan and cetuximab in patients with irinotecan-refractory tumors suggests that cetuximab may circumvent irinotecan resistance. Cells acquire irinotecan resistance by several mechanisms.²³ EGFR inhibition by cetuximab may overcome this resistance by abrogating drug efflux,²³⁻²⁸ restoring apoptosis,²⁹ or impairing DNA-repair activity.^{30,31}

An acne-like or maculopapular rash, a characteristic side effect of EGFR blockade, is due to the role of EGFR in maintaining the integrity of the skin. Response and survival have been shown to be correlated with the severity of the rash in phase 2

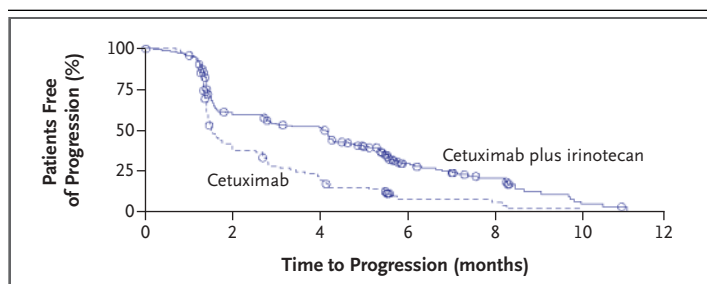


Figure 2. Time to Disease Progression in the Two Study Groups.

The hazard ratio for disease progression in the combination-therapy group as compared with the monotherapy group was 0.54 (95 percent confidence interval, 0.42 to 0.71) ($P < 0.001$ by the log-rank test). The points on the curves represent the dates on which a patient's data were censored.

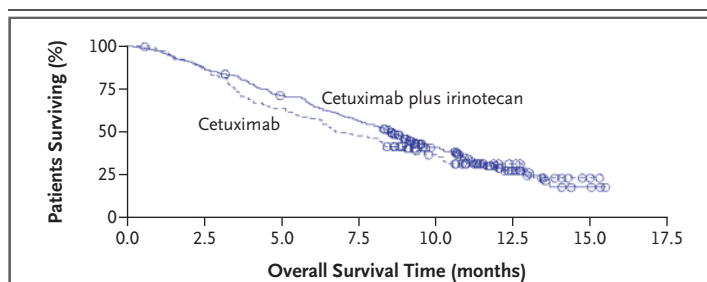


Figure 3. Overall Survival in the Two Study Groups.

The hazard ratio for death in the combination-therapy group as compared with the monotherapy group was 0.91 (95 percent confidence interval, 0.68 to 1.21) ($P = 0.48$ by the log-rank test). The points on the curves represent the dates on which a patient's data were censored.

studies,³² and the correlation is confirmed by our study, although it is based on subgroup analyses. Since no dose-limiting toxicity was observed in phase 1 studies of cetuximab given according to the currently recommended dosage regimen,³³ individualized dose titration based on the occurrence and severity of rash may improve the effectiveness of cetuximab treatment. The rates of incidence of other hematologic and nonhematologic toxic effects in the combination-therapy group were similar to those reported in randomized studies of irinotecan as second-line therapy.^{6,7}

In contrast to the blockade of HER2 by trastuzumab in breast cancer,³⁴ there was no apparent relationship between the efficacy of cetuximab and the level of EGFR in the tumor. A similar observation has been made with gefitinib, another EGFR tyrosine kinase inhibitor.³⁵ Only patients with im-

Table 4. Grade 3 or 4 Adverse Events Related to Treatment.*

Adverse Event	Cetuximab plus Irinotecan (N=212)	Cetuximab Monotherapy (N=115)	P Value
	<i>no. of patients (%)</i>		
Any	138 (65.1)	50 (43.5)	<0.001
Anemia	10 (4.7)	3 (2.6)	0.55
Neutropenia	20 (9.4)	0	<0.001
Thrombocytopenia	1 (0.5)	1 (0.9)	1.00
Diarrhea	45 (21.2)	2 (1.7)	<0.001
Asthenia	29 (13.7)	12 (10.4)	0.49
Acne-like rash	20 (9.4)	6 (5.2)	0.20
Nausea and vomiting	15 (7.1)	5 (4.3)	0.47
Abdominal pain	7 (3.3)	6 (5.2)	0.39
Stomatitis	5 (2.4)	1 (0.9)	0.67
Dyspnea	3 (1.4)	15 (13.0)	<0.001
Fever	5 (2.4)	0	0.17
Hypersensitivity reaction	0	4 (3.5)	0.01
Death	0	0	1.00

* Four patients who were randomly assigned to the combination-therapy group did not receive irinotecan and were thus evaluated for safety in the monotherapy group. Two patients who were randomly assigned to the combination-therapy group did not receive any study medication.

munohistochemical evidence of EGFR expression were included in our study, and therefore whether patients without EGFR expression would benefit from cetuximab is unknown. EGFR expression has not been shown to be a predictor of responsiveness to gefitinib in non-small-cell lung cancer.^{36,37} It is possible that the level of activated, phosphorylated EGFR is more important than the total EGFR level³⁵

or, in lung cancer, the presence of mutations in the ATP-binding site of EGFR,³⁸ in the prediction of efficacy.

Patients with advanced colorectal cancer who receive fluoropyrimidine, irinotecan, and oxaliplatin in combination or sequentially may survive 18 to 21 months. However, once these three standard drugs have failed, there are no accepted treatment options. Therefore, the observed tumor-response rate of 22.9 percent among patients with irinotecan-refractory colorectal cancer is clinically important. Cetuximab compares favorably with oxaliplatin-based therapy in patients with irinotecan-refractory disease. The 22.9 percent rate of response to cetuximab in combination with irinotecan was higher than the response rate reported for oxaliplatin in combination with infused fluorouracil and leucovorin (9.6 percent),⁸ but the median time to progression and the survival time were similar with the two regimens. Furthermore, previous oxaliplatin treatment did not negate any benefit of cetuximab. The one-year survival rates in this group of heavily pretreated patients — 29 percent in the combination-therapy group and 32 percent in the monotherapy group — are encouraging. Moreover, about 48 percent of the patients obtained clinically meaningful disease control.

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APPENDIX

The following investigators participated in the study: the Netherlands — G.S. Liem, H. Goey, C.J. van Groeningen, and R.J.M. van Leendert; United Kingdom — D. Cunningham, L. Samuel, T. Hickish, M. Hill, T. Iveson, J. Ledermann, P. Mainwaring, and J. Cassidy; Germany — C. Bokemeyer, M. Möhler, N. Niederle, H.-J. Schmoll, C. Peschel, and E. Kettner; France — M. Ychou, A. de Gramont, M. Ducreux, M.C. Kaminsky, J.-F. Seitz, D. Khayat, and Y. Becouarn; Austria — W. Scheithauer, H. Ludwig, J. Schüller, H. Zwierzina, H. Samonigg, and H. Hausmaninger; Belgium — E. Van Cutsem, J. van Laethem, H. Bleiberg, and Y. Humblet; Sweden — H. Mellstedt and M. Albertsson; Spain — A. Cervantes Ruipérez, J. Taberero Caturra, E. Diaz-Rubio, P. Gascón Vilaplana, M. Navarro Garcia, and A. Antón Torres; Italy — E. Bajetta, P. Conte, F. de Braud, A. Santoro, S. Siena, S. Artale, F. Grossi, A.R. Bianco, and A. Sobrero; Switzerland — R. Herrmann and C. Sessa; and Norway — S. Dueland.

REFERENCES

- de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18:2938-47.
- 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.]
- Giacchetti S, Perpoint B, Zidani R, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18:136-47.
- Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin

- platin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;22:23-30.
5. 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.
 6. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413-8.
 7. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;352:1407-12. [Erratum, *Lancet* 1998;352:1634.]
 8. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003;21:2059-69.
 9. Messa C, Russo F, Caruso MG, Di Leo A. EGF, TGF- α , and EGF-R in human colorectal adenocarcinoma. *Acta Oncol* 1998;37:285-9.
 10. Porebska I, Harlozinska A, Bojarowski T. Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. *Tumour Biol* 2000;21:105-15.
 11. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995;19:183-232.
 12. Goldstein NS, Armin M. Epidermal growth factor receptor immunohistochemical reactivity in patients with American Joint Committee on Cancer Stage IV colon adenocarcinoma: implications for a standardized scoring system. *Cancer* 2001;92:1331-46.
 13. Mayer A, Takimoto M, Fritz E, Schellander G, Kofler K, Ludwig H. The prognostic significance of proliferating cell nuclear antigen, epidermal growth factor receptor, and mdr gene expression in colorectal cancer. *Cancer* 1993;71:2454-60.
 14. Klapper LN, Kirschbaum MH, Sela M, Yarden Y. Biochemical and clinical implications of the ErbB/HER signaling network of growth factor receptors. *Adv Cancer Res* 2000;77:25-79.
 15. Ciardiello F, Tortora G. A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor. *Clin Cancer Res* 2001;7:2958-70.
 16. Prewett MC, Hooper AT, Bassi R, Ellis LM, Waksal HW, Hicklin DJ. Enhanced anti-tumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res* 2002;8:994-1003.
 17. Saltz L, Rubin MS, Hochster HS, et al. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11 refractory colorectal cancer that expresses epidermal growth factor receptor. *Prog Proc Am Soc Clin Oncol* 2001;20:3a. abstract.
 18. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004;22:1201-8.
 19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16.
 20. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
 21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
 22. Peto R, Peto J. Asymptotically efficient invariant test procedures. *J R Stat Soc [A]* 1972;135:185-206.
 23. Xu Y, Villalona-Calero MA. Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. *Ann Oncol* 2002;13:1841-51.
 24. Chen ZS, Furukawa T, Sumizawa T, et al. ATP-dependent efflux of CPT-11 and SN-38 by the multidrug resistance protein (MRP) and its inhibition by PAK-104P. *Mol Pharmacol* 1999;55:921-8.
 25. Chu XY, Suzuki H, Ueda K, Kato Y, Akiyama S, Sugiyama Y. Active efflux of CPT-11 and its metabolites in human KB-derived cell lines. *J Pharmacol Exp Ther* 1999;288:735-41.
 26. Meyers MB, Merluzzi VJ, Spengler BA, Biedler JL. Epidermal growth factor receptor is increased in multidrug-resistant Chinese hamster and mouse tumor cells. *Proc Natl Acad Sci U S A* 1986;83:5521-5.
 27. Meyers MB, Yu P, Mendelsohn J. Crosstalk between epidermal growth factor receptor and P-glycoprotein in actinomycin D-resistant Chinese hamster lung cells. *Biochem Pharmacol* 1993;46:1841-8.
 28. Naruse I, Ohmori T, Ao Y, et al. Antitumor activity of the selective epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) Iressa (ZD1839) in an EGFR-expressing multidrug-resistant cell line in vitro and in vivo. *Int J Cancer* 2002;98:310-5.
 29. Scwabas GM, Fujioka S, Schmidt C, Fan Z, Evans DB, Chiao PJ. Restoring apoptosis in pancreatic cancer cells by targeting the nuclear factor-kappaB signaling pathway with the anti-epidermal growth factor antibody IMC-C225. *J Gastrointest Surg* 2003;7:37-43.
 30. Bandyopadhyay D, Mandal M, Adam L, Mendelsohn J, Kumar R. Physical interaction between epidermal growth factor receptor and DNA-dependent protein kinase in mammalian cells. *J Biol Chem* 1998;273:1568-73.
 31. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res* 2000;6:2166-74.
 32. Saltz L, Kies MS, Abbruzzese J, Azarnia N, Needle MN. The presence and intensity of the cetuximab-induced acne-like rash predicts increased survival in studies across multiple malignancies. *Prog Proc Am Soc Clin Oncol* 2003;22:204. abstract.
 33. Baselga J, Pfister D, Cooper MR, et al. Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin. *J Clin Oncol* 2000;18:904-14.
 34. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-92.
 35. Ciardiello F, Tortora G. Epidermal growth factor receptor (EGFR) as a target in cancer therapy: understanding the role of receptor expression and other molecular determinants that could influence the response to anti-EGFR drugs. *Eur J Cancer* 2003;39:1348-54.
 36. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003;290:2149-58.
 37. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21:2237-46.
 38. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.

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