ORIGINAL ARTICLE

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

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ABSTRACT

BACKGROUND

Cetuximab is effective in platinum-resistant recurrent or metastatic squamous-cell carcinoma of the head and neck. We investigated the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

METHODS

We randomly assigned 220 of 442 eligible patients with untreated recurrent or metastatic squamous-cell carcinoma of the head and neck to receive cisplatin (at a dose of 100 mg per square meter of body-surface area on day 1) or carboplatin (at an area under the curve of 5 mg per milliliter per minute, as a 1-hour intravenous infusion on day 1) plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles and 222 patients to receive the same chemotherapy plus cetuximab (at a dose of 400 mg per square meter initially, as a 2-hour intravenous infusion, then 250 mg per square meter, as a 1-hour intravenous infusion per week) for a maximum of 6 cycles. Patients with stable disease who received chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects, whichever occurred first.

RESULTS

Adding cetuximab to platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) significantly prolonged the median overall survival from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95% confidence interval, 0.64 to 0.99; P=0.04). The addition of cetuximab prolonged the median progression-free survival time from 3.3 to 5.6 months (hazard ratio for progression, 0.54; P<0.001) and increased the response rate from 20% to 36% (P<0.001). The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19% and 13%, respectively), neutropenia (23% and 22%), and thrombocytopenia (11% in both groups). Sepsis occurred in 9 patients in the cetuximab group and in 1 patient in the chemotherapy-alone group (P=0.02). Of 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths.

CONCLUSIONS

As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck. (ClinicalTrials.gov number, NCT00122460.)

Platinum-based chemotherapy consisting of either cisplatin or carboplatin is the usual first-line treatment for inoperable recurrent or metastatic squamous-cell carcinoma of the head and neck. Cisplatin is often combined with fluorouracil, but the results of this treatment are far from satisfactory.[1]

Head and neck cancer cells often express the epidermal growth factor receptor (EGFR), and its presence is associated with a poor outcome.[2-4] Cetuximab (Erbitux, developed by Merck [Darmstadt], under license from ImClone) is an IgG1 monoclonal antibody that inhibits ligand binding to the EGFR[5-7] and stimulates antibody-dependent cell-mediated cytotoxicity.[8-10] It also enhances the activity of a number of chemotherapeutic agents, including cisplatin.[11]

Cetuximab is effective in recurrent or metastatic squamous-cell carcinoma of the head and neck that progresses despite platinum-containing therapy.[12-14] In first-line therapy, adding cetuximab to cisplatin improves the response rate as compared with cisplatin alone.[15] A combination of platinum, fluorouracil, and cetuximab is also active in first-line treatment.[16] We investigated the efficacy and safety of platinum, fluorouracil, and cetuximab in the first-line treatment of patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

METHODS

PATIENTS

Patients were eligible if they were 18 years of age or older and had histologically or cytologically confirmed recurrent or metastatic squamous-cell carcinoma of the head and neck. Other inclusion criteria included ineligibility for local therapy; at least one lesion that was bidimensionally measurable by computed tomography (CT) or magnetic resonance imaging (MRI); a Karnofsky performance score of 70 or more (on a scale of 0 to 100, with higher scores indicating better performance); adequate hematologic, renal, and hepatic function; and tumor tissue that was available for evaluation of EGFR expression. The main exclusion criteria were surgery or irradiation within the previous 4 weeks, previous systemic chemotherapy unless it was part of multimodal treatment for locally advanced disease that had been completed more than 6 months before study entry, nasopharyngeal carcinoma, and other concomitant anticancer therapies.

The trial protocol was approved by the independent ethics committee of each center and by the authorities in each relevant country. The trial was conducted in accordance with the Declaration of Helsinki. All patients provided oral and written informed consent.

STUDY DESIGN

Patients with previously untreated recurrent or metastatic squamous-cell carcinoma of the head and neck were randomly assigned, in a 1:1 ratio, to receive a platinum agent (either cisplatin or carboplatin) plus fluorouracil, either alone (the chemotherapy-alone group) or in combination with cetuximab (the cetuximab group). Randomization was performed with the use of a centralized interactive voice-response system and permuted blocks and was stratified according to the receipt or nonreceipt of previous chemotherapy and the Karnofsky score (either <80 or ≥80).

The primary end point was overall survival, defined as the time from randomization to death. Secondary end points were progression-free survival (the time from randomization to the first radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomization, whichever came first), the best overall response (a complete response or partial response persisting for at least 4 weeks), disease control (defined as a complete response, a partial response, or stable disease), the time to treatment failure (the time from randomization until the date of the first occurrence of one of the events specified in the protocol as constituting treatment failure), the duration of the response (the time from the first documentation of a complete or partial response until the first occurrence of disease progression or until death), and safety.

The study was designed by the Global Clinical Development Unit in Oncology and the Department of Biostatistics and Data Sciences at Merck (Darmstadt), in collaboration with Dr. Vermorken. Merck sponsored the trial and performed the statistical analyses. Data were collected by the investigators at each center. All authors had access to all the data; Dr. Vermorken vouches for the completeness and accuracy of the data and analyses. The article was written by Dr. Vermorken, with the assistance of an independent medical writer funded by Merck, and was reviewed by all coauthors and the sponsor.

TREATMENT

The patients received either cisplatin (at a dose of 100 mg per square meter of body-surface area as a 1-hour intravenous infusion on day 1) or carboplatin (at an area under the curve of 5 mg per milliliter per minute, as a 1-hour intravenous infusion on day 1) and an infusion of fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks. The use of cisplatin or carboplatin was at the discretion of the investigator. Cetuximab was administered at an initial dose of 400 mg per square meter given as a 2-hour intravenous infusion, followed by subsequent weekly doses of 250 mg per square meter given as a 1-hour intravenous infusion, ending at least 1 hour before the start of chemotherapy. Dose modifications of chemotherapy and cetuximab were permitted according to protocol-specified criteria.

Patients received a maximum of six cycles of chemotherapy. Patients with unacceptable toxic effects of one of the study drugs received only the tolerated drugs until disease progression. Patients who discontinued treatment before disease progression remained in the study and continued to undergo assessments at 6-week intervals until disease progression. After a maximum of six cycles of chemotherapy, patients in the cetuximab group who had at least stable disease received cetuximab monotherapy until the disease progressed or there were unacceptable toxic effects, whereas patients in the chemotherapy-alone group received no further active treatment but remained in the study until disease progression.

ASSESSMENT

Tumor responses were assessed by CT or MRI at baseline and at 6-week intervals after the start of treatment until disease progression. Imaging within 4 weeks after screening was acceptable, and imaging could be performed whenever disease progression was suspected. Modified World Health Organization criteria were used to determine tumor response and disease progression.[12] Concomitant medications and adverse events were monitored weekly throughout the study in the cetuximab group and at the start of every cycle in the chemotherapy-alone group. After disease progression, survival status and any further anticancer treatments were documented at follow-up visits every 3 months.

STATISTICAL ANALYSIS

Assuming a median survival of 7 months among patients with recurrent or metastatic disease and an approximate increase of 36% in median survival with the addition of cetuximab to platinum–fluorouracil chemotherapy, we calculated that an event-driven analysis after 340 deaths would provide the study with a power of 80% to detect a difference at a two-sided, 5% significance level. Random assignment to study groups of a total of 420 patients within 20 months would lead to an estimated total study duration of 34 months (with the assumption that 5% of the patients would be lost to follow-up). The data cutoff point for the study was March 12, 2007.

All patients were randomly assigned to receive a study treatment; efficacy analyses were conducted in the intention-to-treat population. To adjust for multiple comparisons, a hierarchical order of the end points for efficacy was specified (i.e., overall survival time, progression-free survival time, best overall response, disease control, time to treatment failure, and duration of response), which would allow for confirmatory conclusions in the case of significant P values. The safety population included all patients who received any dose of any study medication. Safety data were monitored by an independent data safety monitoring board. Further analyses, such as subgroup analyses, were purely exploratory. All subgroup analyses were stipulated in the protocol.

Time-to-event variables were compared by means of the use of the stratified log-rank test with the strata used for randomization. The Cox regression method, stratified according to the randomization categories, was used to calculate the hazard ratios. The model was extended by inclusion of an interaction variable for subgroup status and treatment effect. One significant interaction would be expected on the basis of chance alone.

All statistical tests comparing treatment groups were two-sided, with an alpha level of 5% considered to indicate statistical significance. The interquartile range (quartiles 1 to 3) was provided for medians. In a secondary multivariate analysis of overall survival time, a Cox regression model with stepwise variable selection was used to identify variables of potential prognostic relevance. The significance levels used for determining the entry and removal of variables from the

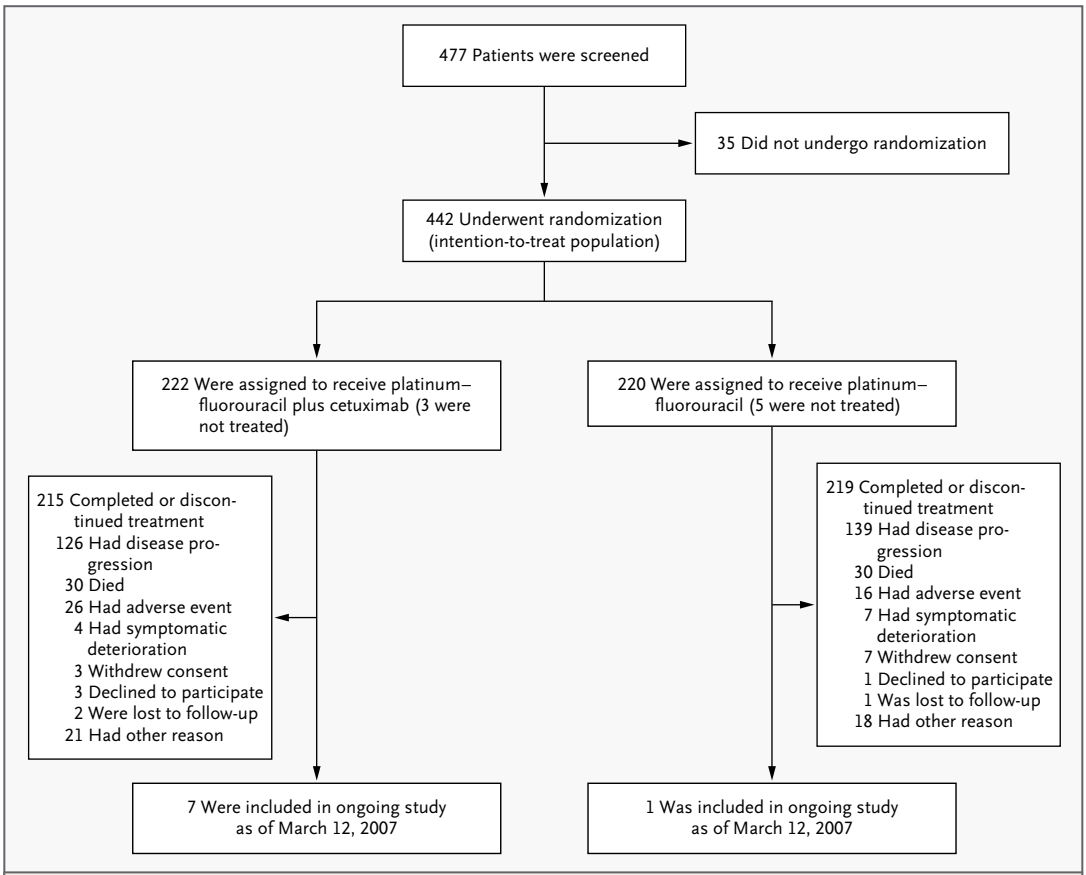

Figure 1. Enrollment and Outcomes.

model were P=0.15 and P=0.40, respectively. The stratification factors were forced into the model, and the treatment factor was added at the end of the selection process. Cox regression modeling with a time-varying covariate analysis was performed to evaluate the association between the development of skin reactions and overall survival time[17] in patients receiving cetuximab in whom disease progression did not develop during the first cycle of chemotherapy (i.e., within 21 days after study entry).

RESULTS

CHARACTERISTICS OF THE PATIENTS

Between December 21, 2004, and December 30, 2005, a total of 477 patients underwent screening at 81 centers in 17 European countries (Fig. 1). Of these 477 patients, 41 were not enrolled: 30 patients did not meet inclusion or exclusion criteria, 3 died, 3 withdrew consent, and 5 were not enrolled for other reasons. In addition to the 436 eligible patients, 6 ineligible patients were randomly assigned to study groups, resulting in a total of 442 patients who underwent randomization (the intention-to-treat population). Eight patients (three in the cetuximab group and five in the chemotherapy-alone group) did not receive any treatment. Thus, the safety population comprised 434 patients.

The two treatment groups were well balanced with respect to the baseline characteristics of the patients (Table 1). Cisplatin was administered as the initial platinum-based treatment in 149 patients (67%) in the cetuximab group and in 135 patients (61%) in the chemotherapy-alone group. One patient in the safety population received neither cisplatin nor carboplatin. During treatment, 10% of the patients receiving cisplatin–fluorouracil plus cetuximab and 15% of the patients re-

Table 1. Baseline Characteristics of the Patients.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)
Sex — no. (%)		
Male	197 (89)	202 (92)
Female	25 (11)	18 (8)
Age		
Median age — yr	56	57
<65 yr — no. (%)	183 (82)	182 (83)
≥65 yr — no. (%)	39 (18)	38 (17)
Karnofsky score		
Median score	80	80
Interquartile range	80–90	80–90
<80 — no. (%)	27 (12)	25 (11)
≥80 — no. (%)	195 (88)	195 (89)
Duration of disease — mo†		
Median	15.5	15.8
Interquartile range	10.3–27.0	9.5–33.5
Primary tumor site — no. (%)		
Oropharynx	80 (36)	69 (31)
Hypopharynx	28 (13)	34 (15)
Larynx	59 (27)	52 (24)
Oral cavity	46 (21)	42 (19)
Other	9 (4)	23 (10)
Extent of disease — no. (%)		
Only locoregionally recurrent	118 (53)	118 (54)
Metastatic with or without locoregional recurrence	104 (47)	102 (46)
Histologic type — no. (%)		
Well differentiated	35 (16)	40 (18)
Moderately differentiated	93 (42)	101 (46)
Poorly differentiated	46 (21)	46 (21)
Not specified or missing	48 (22)	33 (15)
Previous treatment — no. (%)		
Chemotherapy	90 (41)	80 (36)
Radiotherapy	189 (85)	190 (86)
Percentage of EGFR-detectable cells — no. (%)‡		
0	3/209 (1)	5/204 (2)
>0 to <40	32/209 (15)	32/204 (16)
≥40	174/209 (83)	167/204 (82)
Missing data	13/222 (6)	16/220 (7)

* Percentages may not sum to 100 because of rounding. EGFR denotes epidermal growth factor receptor.
† The duration of disease is the time from initial diagnosis to informed consent.
‡ These percentages are for patients in whom EGFR data were available.

ceiving cisplatin–fluorouracil alone could not tolerate cisplatin and were switched to carboplatin. Of the 413 tumors that were tested by immunohistochemical analysis, 98% had detectable EGFR, and more than 80% had 40% or more EGFR-positive cells.

COMPLIANCE

The median duration of treatment with cetuximab was 18 weeks (interquartile range, 8 to 29). For 84% of the patients, the relative dose intensity of cetuximab (the amount given over a specified time as a proportion of the planned amount) was 80% or more after the initial dose of 400 mg per square meter. A total of 100 patients received cetuximab monotherapy during the maintenance period, with a median duration of treatment of 11 weeks. For 82% of the patients, the relative dose intensity of cetuximab was 80% or more during this maintenance period. Patients in the cetuximab group received a median of five cycles of chemotherapy, and patients in the chemotherapy-alone group received a median of four cycles.

The median duration of treatment with cisplatin was 15 weeks (interquartile range, 6 to 19) in the cetuximab group and 12 weeks (interquartile range, 6 to 19) in the chemotherapy-alone group. For 89% of the patients in the cetuximab group and 86% of the patients in the chemotherapy-alone group, the relative dose intensity of cisplatin was 80% or more.

The median duration of treatment with carboplatin was 18 weeks (interquartile range, 10 to 19) in the cetuximab group and 13 weeks (interquartile range, 9 to 18) in the chemotherapy-alone group. The relative dose intensity of carboplatin was 80% or more in 93% of the patients in the cetuximab group and in 80% of the patients in the chemotherapy-alone group.

The median duration of treatment with fluorouracil was 17 weeks (interquartile range, 8 to 18) in the cetuximab group and 13 weeks (interquartile range, 6 to 18) in the chemotherapy-alone group; the relative dose intensity of fluorouracil was 80% or more in 83% and 84% of patients in the two groups, respectively. Fourteen patients (6%) in the chemotherapy-alone group received cetuximab after the conclusion of the study.

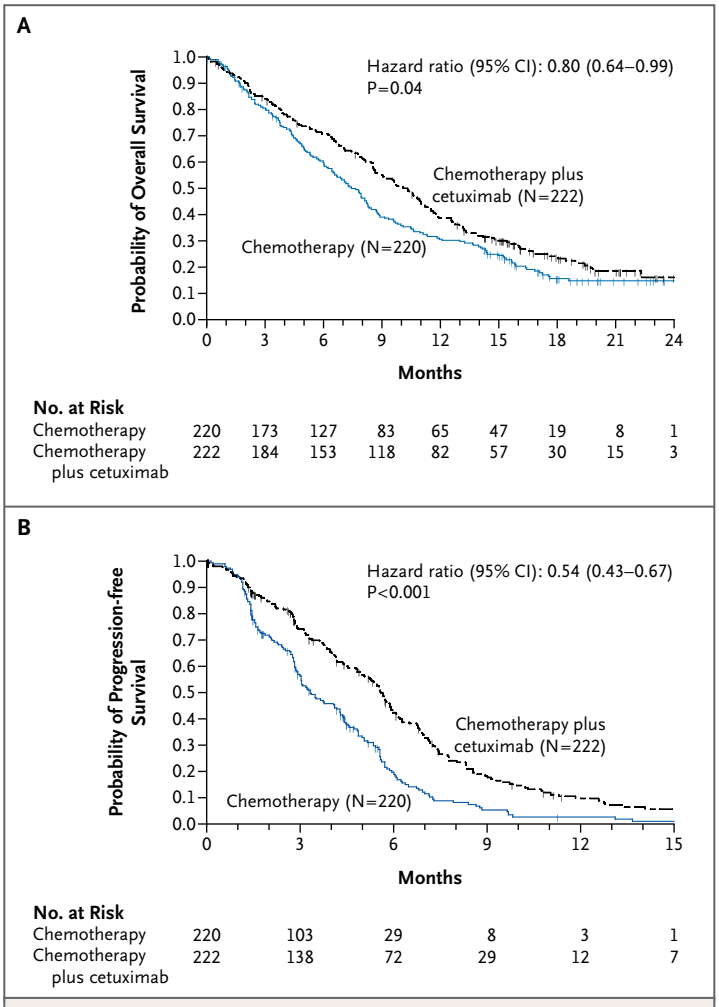

Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group.

EFFICACY

The median overall survival was 10.1 months (95% confidence interval [CI], 8.6 to 11.2) in the cetuximab group and 7.4 months (95% CI, 6.4 to 8.3) in the chemotherapy-alone group (hazard ratio for death, 0.80; 95% CI, 0.64 to 0.99; P=0.04) (Fig. 2A and Table 2). The median follow-up was 19.1 months in the cetuximab group and 18.2 months in the chemotherapy-alone group. Among the patients who were alive at the time of the analysis, the minimum follow-up was 12.9 months and the maximum follow-up was 26.0 months. Sixteen patients (4%) withdrew consent or were lost to follow-up.

Table 2. Responses to Treatment and Survival.*

Variable	Cetuximab plus Platinum–Fluorouracil (N=222)	Platinum–Fluorouracil Alone (N=220)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Survival — mo†				
Overall	10.1 (8.6–11.2)	7.4 (6.4–8.3)	Hazard ratio, 0.80 (0.64–0.99)	0.04‡
Progression-free	5.6 (5.0–6.0)	3.3 (2.9–4.3)	Hazard ratio, 0.54 (0.43–0.67)	<0.001‡
Best response to therapy — %				
Overall	36 (29–42)	20 (15–25)	Odds ratio, 2.33 (1.50–3.60)	<0.001§
Disease control¶	81 (75–86)	60.0 (53–67)	Odds ratio, 2.88 (1.87–4.44)	<0.001§
Time to treatment failure — mo†	4.8 (4.0–5.6)	3.0 (2.8–3.4)	Hazard ratio, 0.59 (0.48–0.73)	<0.001‡
Duration of response — mo‖	5.6 (4.7–6.0)	4.7 (3.6–5.9)	Hazard ratio, 0.76 (0.50–1.17)	0.21‡

* Data in the treatment columns are median (95% CI). The P values, hazard ratios, and odds ratios are stratified according to receipt or nonreceipt of previous chemotherapy and the Karnofsky performance score at randomization.
† The number of months was estimated with the use of the Kaplan–Meier method.
‡ The P value was calculated with the use of the log-rank test.
§ The P value was calculated with the use of the Cochran–Mantel–Haenszel test.
¶ Disease control includes complete response, partial response, and stable disease.‖ Time to treatment failure was defined as the time from randomization until the first occurrence of one of the following events: disease progression as assessed by the investigator, discontinuation of treatment because of disease progression, discontinuation of treatment because of an adverse event, initiation of any new anticancer therapy, or withdrawal of consent or death within 60 days after the final tumor assessment or randomization.
‖ Data on the duration of response were available for 62 patients in the cetuximab group and 36 patients in the chemotherapy-alone group; data on disease progression in these patients were available at the time of the analysis. The number of months was estimated with the use of the Kaplan–Meier method.

Median progression-free survival was 5.6 months in the cetuximab group and 3.3 months in the chemotherapy-alone group (hazard ratio for progression, 0.54; 95% CI, 0.43 to 0.67; P<0.001) (Fig. 2B and Table 2). The addition of cetuximab to platinum–fluorouracil chemotherapy was also associated with significant increases in the overall response rate, disease-control rate, and time to treatment failure as compared with platinum–fluorouracil chemotherapy alone (Table 2). The duration of the response in the two groups did not differ significantly. Among the 100 patients who received cetuximab as maintenance treatment, the median progression-free survival was 12 weeks from the start of maintenance treatment. There were two tumor responses during cetuximab maintenance treatment.

Preplanned multivariate analysis identified the Karnofsky score as having the greatest prognostic relevance for overall survival time. A Karnofsky score of 80 or more reduced the risk of death by 49% as compared with a Karnofsky score of less than 80 (hazard ratio, 0.51; 95% CI, 0.37 to 0.69; P<0.001). There was no significant difference in survival between patients with metastatic or recurrent and metastatic disease and those with only recurrent locoregional disease (P=0.06). The treatment effect seen in the multivariate model (hazard ratio for progression, 0.79; 95% CI, 0.64 to 0.97; P=0.03) confirmed the effect seen in the primary analysis. There was no significant association between the appearance of a rash and survival (hazard ratio for death, 0.77; 95% CI, 0.55 to 1.09; P=0.14 by the score test).

SUBGROUP ANALYSES

Protocol-defined subgroup analyses showed that the beneficial effects of adding cetuximab to platinum–fluorouracil chemotherapy on overall survival and progression-free survival were evident in most subgroups analyzed (Fig. 3 and 4).

SAFETY

No safety concerns were identified at the two meetings of the data safety monitoring board that were held during the study. The safety profile of the study treatment was consistent with that expected for the agents used. For the most part, there was no significant difference in the overall incidence of grade 3 or 4 adverse events between

Subgroup	No. of Patients	Median Overall Survival (Cetuximab plus Chemotherapy vs. Chemotherapy)	Hazard Ratio (95% CI)
		mo	
All patients	442	10.1 vs. 7.4	0.80 (0.64–0.99)
Age			
<65 yr	365	10.5 vs. 7.3	0.74 (0.59–0.94)
≥65 yr	77	9.1 vs. 7.8	1.07 (0.65–1.77)
Karnofksy performance score			
<80	52	6.3 vs. 4.4	1.14 (0.64–2.04)
≥80	390	10.6 vs. 7.9	0.75 (0.60–0.94)
Platinum regimen			
Cisplatin	284	10.6 vs. 7.3	0.69 (0.53–0.91)
Carboplatin	149	9.7 vs. 8.3	0.98 (0.69–1.41)
Previous treatment			
Neoadjuvant chemotherapy	57	10.7 vs. 6.3	0.82 (0.46–1.49)
Radiochemotherapy	129	8.6 vs. 7.5	0.90 (0.61–1.34)
Primary tumor site			
Oral cavity	88	11.0 vs. 4.4	0.42 (0.26–0.67)
Oropharynx	149	10.9 vs. 7.9	0.85 (0.58–1.23)
Larynx	111	8.6 vs. 8.4	0.99 (0.65–1.51)
Hypopharnyx	62	8.4 vs. 8.9	1.14 (0.64–2.04)
Tumor grade			
Well- or moderately differentiated	269	9.5 vs. 6.5	0.72 (0.55–0.94)
Poorly differentiated	92	10.8 vs. 9.4	1.00 (0.62–1.60)
Baseline quality-of-life score			
≤Median	129	7.4 vs. 5.9	0.86 (0.59–1.24)
>Median	98	13.9 vs. 9.2	0.70 (0.43–1.12)
Percentage of EGFR-detectable cells			
>0 to <40%	64	10.9 vs. 7.8	0.72 (0.40–1.28)
≥40%	341	10.1 vs. 7.1	0.75 (0.59–0.95)

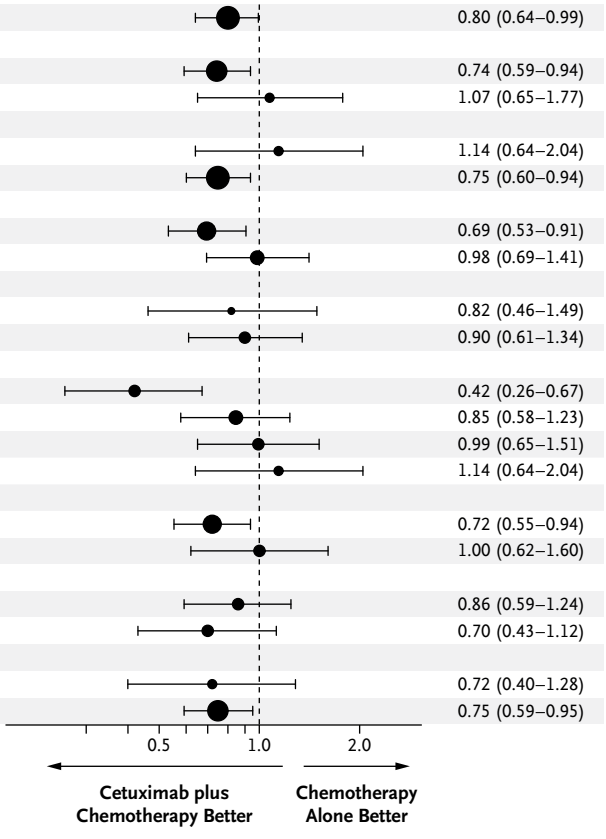

Figure 3. Hazard Ratios for Death.

Previous treatment may have included neoadjuvant chemotherapy, radiochemotherapy, or both. Only the interaction between the treatment and the primary tumor site was significant (P=0.03). The sizes of the circles are proportional to the number of events.

the groups. However, there were 9 cases of sepsis in the cetuximab group, as compared with 1 case in the chemotherapy-alone group (P=0.02), and there were 11 cases of hypomagnesemia in the cetuximab group, as compared with 3 cases in the chemotherapy-alone group (P=0.05) (Table 3).

Grade 3 skin reactions were seen in 9% of the patients who received cetuximab. No grade 4 skin reactions were reported. There were four grade 3 infusion-related reactions (two cases of allergy or anaphylaxis, one of dyspnea, and one of hypotension) and two grade 4 reactions (allergy or anaphylaxis in both cases) among patients receiving cetuximab. There were no infusion-related reactions in the chemotherapy-alone group. Adverse events led to discontinuation of chemotherapy or cetuximab in approximately 20% of the patients in each group. Ten deaths (three in the cetuximab group and seven in the chemotherapy-alone group) were considered by the investigators to be treatment-related. No deaths were considered to be related to cetuximab by the investigators while they were still unaware of the treatment assignment.

DISCUSSION

This phase 3, randomized trial of first-line treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck showed a significant increase in overall survival with the addition of

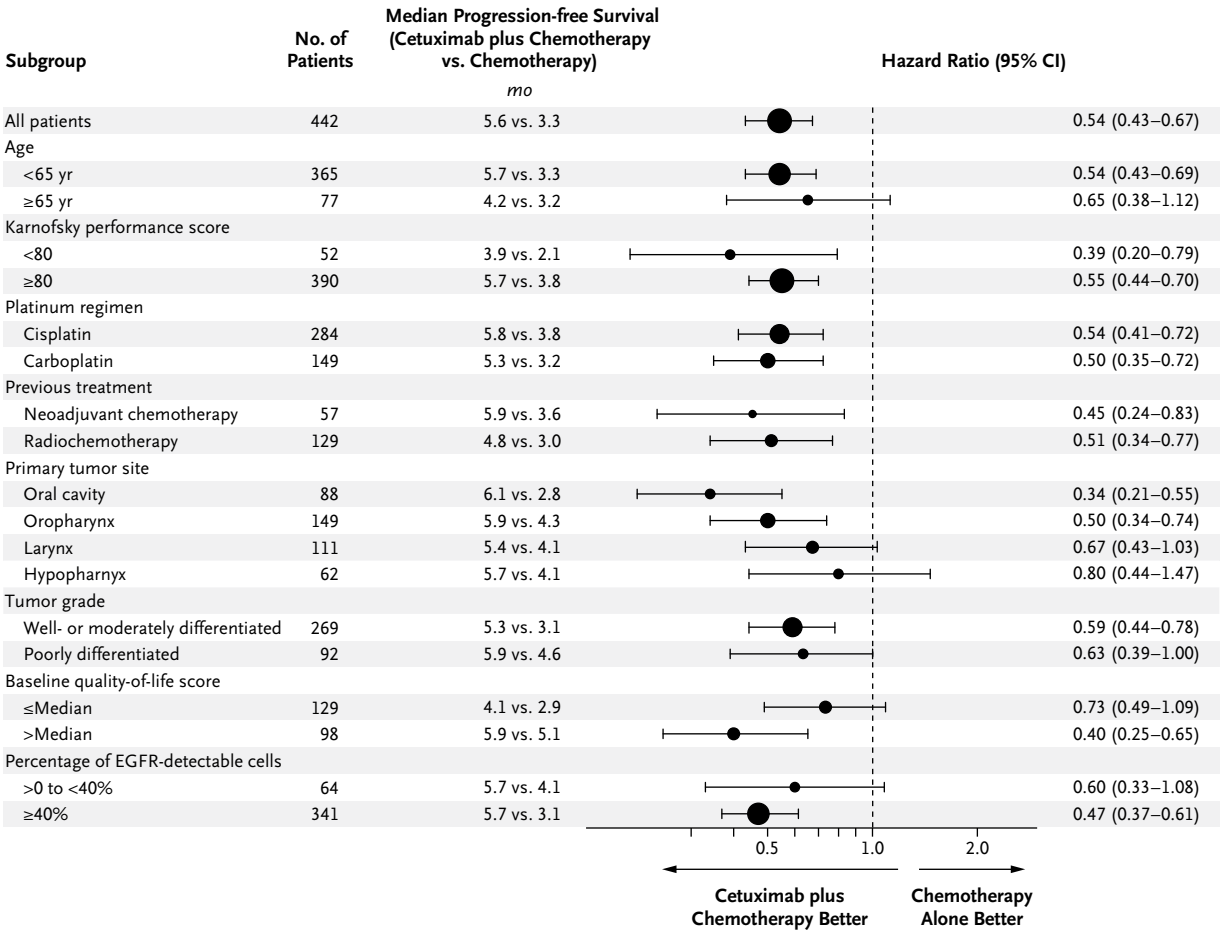

Figure 4. Hazard Ratios for Disease Progression.

Previous treatment may have included neoadjuvant chemotherapy, radiochemotherapy, or both. Only the interaction between the treatment and primary tumor site was significant (P=0.02). The sizes of the circles are proportional to the number of events.

cetuximab to standard doses of platinum–fluorouracil chemotherapy. The addition of cetuximab was associated with a 2.7-month increase in the median survival and a significant 20% reduction in the relative risk of death, as compared with platinum–fluorouracil chemotherapy alone. Secondary efficacy end points were also significantly improved in the cetuximab group, with a 2.3-month prolongation of progression-free survival (a 46% reduction in the risk of disease progression), an 83% increase in the response rate, and a 41% reduction in the risk of treatment failure.

The median overall survival of 7.4 months in the chemotherapy-alone group is consistent with the results of other randomized trials.[18,19] The best overall response rate observed in this study (20%) was at the lower end of the range usually reported for cisplatin-based therapy; this might be due to the fact that approximately one third of the patients received carboplatin, which is associated with lower response rates than cisplatin.[18,20]

Subgroup analyses indicated that the benefit of adding cetuximab to platinum–fluorouracil chemotherapy was evident in most of the subgroups. The hazard ratios for progression-free survival showed a uniformly positive effect of adding cetuximab in all subgroups, with hazard ratios ranging from 0.34 to 0.80. There was a significant interaction with the primary tumor site, but because of repeated testing, this result could be due to

Table 3. Grade 3 or 4 Adverse Events in the Safety Population.*

Event	Cetuximab plus Platinum–Fluorouracil (N=219)		Platinum–Fluorouracil Alone (N=215)		P Value†
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4	
	number of patients (%)				
Any event	179 (82)	67 (31)	164 (76)	66 (31)	0.19
Neutropenia	49 (22)	9 (4)	50 (23)	18 (8)	0.91
Anemia	29 (13)	2 (1)	41 (19)	2 (1)	0.12
Thrombocytopenia	24 (11)	0	24 (11)	3 (1)	1.00
Leukopenia	19 (9)	4 (2)	19 (9)	5 (2)	1.00
Skin reactions‡	20 (9)	0	1 (<1)	0	<0.001
Hypokalemia	16 (7)	2 (1)	10 (5)	1 (<1)	0.31
Cardiac events§	16 (7)	11 (5)	9 (4)	7 (3)	0.22
Vomiting	12 (5)	0	6 (3)	0	0.23
Asthenia	11 (5)	1 (<1)	12 (6)	1 (<1)	0.83
Anorexia	11 (5)	2 (1)	3 (1)	1 (<1)	0.05
Hypomagnesemia	11 (5)	8 (4)	3 (1)	1 (<1)	0.05
Febrile neutropenia	10 (5)	2 (1)	10 (5)	4 (2)	1.00
Dyspnea	9 (4)	2 (1)	17 (8)	5 (2)	0.11
Pneumonia	9 (4)	3 (1)	4 (2)	1 (<1)	0.26
Hypocalcemia	9 (4)	5 (2)	2 (1)	0	0.06
Sepsis (including septic shock)	9 (4)	6 (3)	1 (<1)	1 (<1)	0.02
Tumor hemorrhage	3 (1)	2 (1)	6 (3)	4 (2)	0.33
Decreased performance status	2 (1)	1 (<1)	4 (2)	4 (2)	0.45
Respiratory failure	1 (<1)	0	5 (2)	4 (2)	0.12

* Grade 3 or 4 adverse events are listed if they were reported in 5% or more of patients in either treatment group, and grade 4 adverse events are listed if they were reported in 1% or more of patients in either group.
† The P values are for the differences between the treatment groups for grades 3 and 4 combined.
‡ Skin reactions were coded with the use of preferred terms from the *Medical Dictionary for Regulatory Activities*. These terms include acne pustular, acne, cellulitis, dermatitis acneiform, dry skin, erysipelas, erythema, face edema, folliculitis, growth of eyelashes, hair growth abnormal, hypertrichosis, nail-bed infection, nail-bed inflammation, nail disorder, nail infection, paronychia, pruritus, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash, skin exfoliation, skin hyperpigmentation, skin necrosis, staphylococcal scalded skin syndrome, telangiectasia, wound necrosis, and xerosis. Grade 2 skin reactions were observed in 70 patients receiving platinum–fluorouracil plus cetuximab and in 6 patients receiving platinum–fluorouracil alone.
§ "Cardiac events" was a special adverse-event category comprising five medical conditions: arrest, arrhythmia, congestive heart failure, ischemia or infarction, and sudden death. The main grade 3 or 4 cardiac events in this study for patients receiving platinum–fluorouracil plus cetuximab and those receiving platinum–fluorouracil alone were congestive heart failure (four patients and one patient, respectively), infarction and ischemia (seven patients and two patients), and sudden death (three patients and one patient).

chance. Such subgroup analyses must be interpreted cautiously[21]; the results do not allow us to state with certainty that some groups did not benefit or to speculate on the degree of benefit.

Compliance with cetuximab was good: a relative dose intensity of 80% or more was achieved in 84% of the patients who received cetuximab after the initial dose of 400 mg per square meter and in 82% of the patients who received cetuximab as maintenance therapy. Compliance with chemotherapy was similar in the two groups, indicating that the addition of cetuximab did not affect the tolerability of the standard treatment.

The adverse-event profile in the chemotherapy-

alone group was typical of that for the combination of platinum plus fluorouracil[18,19] and was not affected by the addition of cetuximab, except that there were 9 cases of sepsis in the cetuximab group, as compared with 1 case in the chemotherapy-alone group. The main additional grade 3 or 4 adverse events, including skin reactions, were consistent with the side-effect profile of cetuximab.

This trial and an earlier randomized trial in which cetuximab was combined with cisplatin[15] showed that cetuximab was effective in combination with platinum-based regimens for recurrent or metastatic squamous-cell carcinoma of the head and neck. Since the introduction of cisplatin for the treatment of recurrent or metastatic squamous-cell carcinoma of the head and neck approximately 30 years ago, there has been little improvement in survival among patients with this disease.[1,22] Our finding that the combination of platinum, fluorouracil, and cetuximab significantly improved survival as compared with platinum and fluorouracil alone is therefore notable.

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REFERENCES

1. Schantz SP, Harrison LB, Forastiere A. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita VT, Hellman SA, Rosenberg SA, eds. Cancer: principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins, 2001: 797-860.
2. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst 1998;90:824-32.
3. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. J Clin Oncol 2006;24:4170-6.
4. Temam S, Kawaguchi H, El-Naggar AK, et al. Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. J Clin Oncol 2007;25:2164-70.
5. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res 1995;1:1311-8.
6. Li S, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P, Ferguson KM. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. Cancer Cell 2005;7:301-11.
7. Sato JD, Kawamoto T, Le AD, Mendelsohn J, Polikoff J, Sato GH. Biological effects in vitro of monoclonal antibodies to human epidermal growth factor receptors. Mol Biol Med 1983;1:511-29.
8. Kang X, Patel D, Ng S, Melchoir M, Ludwig D, Hicklin D. High affinity Fc receptor binding and potent induction of antibody-dependent cellular cytotoxicity (ADCC) *in vitro* by anti-epidermal growth factor receptor antibody cetuximab. J Clin Oncol 2007;25:Suppl:128s. abstract.
9. Kimura H, Sakai K, Arao T, Shimoyama T, Tamura T, Nishio K. Antibody-dependent cellular cytotoxicity of cetuximab against tumor cells with wild-type or mutant epidermal growth factor receptor. Cancer Sci 2007;98:1275-80.
10. Zhang W, Gordon M, Schultheis AM, et al. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. J Clin Oncol 2007;25:3712-8.
11. Fan Z, Baselga J, Masui H, Mendelsohn J. Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. Cancer Res 1993;53:4637-42.
12. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171-7.
13. Baselga J, Trigo JM, Bourhis J, et al. Phase ll multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23:5568-77.
14. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23:5578-87.
15. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 2005;23:8646-54. [Erratum, J Clin Oncol 2006;24:724.]
16. Bourhis J, Rivera F, Mesia R, et al. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2006; 24:2866-72.
17. Collett D. Modelling survival data in medical research. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC Press, 2003:49-51.
18. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992;10: 1245-51.
19. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10:257-63.

20. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. Ann Oncol 1998;9:13-21. [Erratum, Ann Oncol 1998;9:341.]
21. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.
22. Wittes RE, Cvitkovic E, Shah J, Gerold FP, Strong EW. CIS-dichlorodiammineplatinum(II) in the treatment of epidermoid carcinoma of the head and neck. Cancer Treat Rep 1977;61:359-66.