Overview of the Efficacy of Cetuximab in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck in Patients Who Previously Failed Platinum-based Therapies

Jan. B. Vermorken, MD, PhD[1]
Roy S. Herbst, MD, PhD[2]
Xavier Leon, MD, PhD[3]
Nadia Amellal, MD[4]
Jose Baselga, MD[5]

[1] Department of Medical Oncology, University Hospital Antwerp, Edegem, Belgium.

[2] Thoracic Head and Neck Medical Clinic, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[3] Department of Otolaryngology, Hospital de la Sant Creu I de Sant Pau, Barcelona, Spain.

[4] Merck KGaA, Paris, France.

[5] Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain.

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Address for reprints: Jan B. Vermorken, MD, PhD, Department of Medical Oncology, University Hospital Antwerpen, Wilrijkstraat 10, B-2650 Edegem, Belgium; Fax: (011) 32 3 825 05 64; E-mail: jan.b.vermorken@uza.be

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BACKGROUND. The epidermal growth factor receptor (EGFR) inhibitor cetuximab is active in recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). The activity of cetuximab was compared with that of commonly used treatments in this setting.

METHODS. All patients had recurrent and/or metastatic SCCHN and had progressed on cisplatin- or carboplatin-based chemotherapy. Efficacy data from 3 prospective studies (n = 278 patients) that administered cetuximab as a single agent (n = 103 patients) or combined with either cisplatin/carboplatin (n = 96 patients) or cisplatin (n = 79 patients) were compared with the results from a retrospective study of patients who received various second-line treatments (all treatments including best supportive care only, n = 151 patients; chemotherapy, n = 43 patients). Safety data considered were only those from the cetuximab studies.

RESULTS. Over the 3 cetuximab trials, overall response rates from 10% to 13% and disease control rates from 46% to 56% were observed. The median time to disease progression ranged between 2.2 months and 2.8 months, and the median overall survival ranged between 5.2 months and 6.1 months. No patients who progressed on cetuximab alone responded to additional platinum. These survival data compared favorably with those from the retrospective study (median survival, 3.4 months [n = 151 patients] and 3.6 months [n = 43 patients]). Cetuximab-based treatments generally were tolerated well, and cetuximab did not increase the side effects associated with platinum therapy.

CONCLUSIONS. Cetuximab has the potential to prolong survival in patients with recurrent and/or metastatic SCCHN who fail on platinum therapy compared with various second-line therapies. Cetuximab did not increase the toxicities associated with chemotherapy. The results obtained by treatment with cetuximab alone after platinum failure did not appear to differ from the results obtained by reintroducing platinum in combination with cetuximab. ***Cancer*** **2008;112:2710–9.**

KEYWORDS: cetuximab, squamous cell carcinoma of the head and neck, head and neck cancer, cisplatin, carboplatin, second-line, epidermal growth factor receptor.

Worldwide, cancers of the head and neck—primarily tumors of the oral cavity, pharynx, and larynx—account for >5% of all malignancies. In 2002, there were in excess of 500,000 new diag-

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noses and >300,000 deaths attributed to this disease.[1] Most head and neck cancers, approximately 90% in Western societies, are squamous cell carcinomas (SCCHN). The prognosis depends primarily on disease stage and performance status at the time of diagnosis.[2,3]

The currently available treatment options for recurrent and/or metastatic disease are limited. Depending on the extent of disease and the performance status of the patient, they are reirradiation, salvage surgery, chemotherapy, radiotherapy plus chemotherapy (chemoradiotherapy), and best supportive care (BSC). Chemotherapy is generally the treatment of choice when reirradiation is no longer possible. Methotrexate and cisplatin are used commonly in this setting. Patients who receive first-line platinum-based regimens for recurrent and/or metastatic disease generally have a survival of 6 months to 9 months.[4,5] In patients who have progressive disease (PD) while they are receiving platinum-based regimens, the projected median survival falls to approximately 3.5 months.[6,7] Further active therapies, such as taxane- and vinorelbine-based regimens, may be considered in patients with recurrent and/or metastatic disease who have a good performance status.[8–10] However, at this point, many patients will receive only BSC.

Because current treatment options are so limited, there is a clear need for new therapies for patients with recurrent and/or metastatic SCCHN. Molecular-targeted therapies have attracted attention as potential candidates for the treatment of head and neck cancers. Among such agents are those that target the epidermal growth factor receptor (EGFR).[11] EGFR generally is expressed at high levels in SCCHN[12–14] and is associated with a poor prognosis in terms of disease-free survival and overall survival.[13,15]

Cetuximab (Erbitux; Merck KGaA, Darmstadt, Germany) is an immunoglobulin G1 monoclonal antibody that was designed specifically to block human EGFR signaling by binding irreversibly, and with higher affinity than its natural ligands, to the extracellular domain of the receptor.[16] This binding stimulates EGFR internalization and degradation, which results in receptor down-regulation. Furthermore, occlusion of the ligand-binding site by cetuximab competitively inhibits endogenous ligand binding, thereby preventing dimerization and subsequent activation of the intrinsic receptor tyrosine kinase activity.[17–20]

In combination with radiotherapy, cetuximab has demonstrated important activity in patients with locally advanced SCCHN.[21,22] In a randomized Phase III study, the addition of cetuximab to radiotherapy significantly prolonged overall survival by nearly 20 months versus radiotherapy alone (49 months vs 29.3 months; $P = .03$).[22] The hazard ratio was 0.74, representing a 26% reduction in the risk of death. In addition, the risk of locoregional recurrence was reduced by 32% in the cetuximab plus radiotherapy arm.

Cetuximab also has demonstrated activity against recurrent and/or metastatic disease in the first-line setting when given in combination with cisplatin[23] and with cisplatin or carboplatin plus 5-fluorouracil.[24,25] When initial platinum-based therapy has failed, encouraging results have been reported in patients with recurrent and/or metastatic SCCHN for cetuximab both as monotherapy[26,27] and in combination with either cisplatin or carboplatin.[28–31]

The objective of the analysis reported here was to determine more precisely the scope of cetuximab activity in recurrent and/or metastatic SCCHN in patients who progressed on platinum-based therapy by comparing the intention-to-treat efficacy data from 3 Phase II cetuximab studies with a retrospective study of a similar group of patients who were receiving various types of treatment outside an investigational setting.[6,7,26–31]

MATERIALS AND METHODS

Study Designs

This analysis compared data from 3 prospective Phase II studies with cetuximab in patients with recurrent and/or metastatic SCCHN who progressed on platinum-based therapy,[27,28,30] all of which followed an open, multicenter design, with data from a retrospective study of various second-line treatments in a similar group of patients.[6,7] The 3 prospective studies were designed to investigate the efficacy and safety of either cetuximab monotherapy or cetuximab in combination with cisplatin or carboplatin. The principles of the study designs and their key inclusion and exclusion criteria are presented in Table 1; full details are available in the respective publications. Criteria for platinum resistance in each of the studies are shown in Table 2.

With respect to the 3 prospective studies, the individual protocols and amendments were approved by independent ethics committees in each country. The studies were conducted in accordance with the Declaration of Helsinki (1996), and all patients provided written informed consent. In the case of the retrospective study, because data were collected retrospectively in an anonymous fashion from patient files, neither informed consent nor ethical approval was necessary. However, an independent ethics committee in Italy approved the protocol.

TABLE 1
Study Design With Key Inclusion and Exclusion Criteria

Variable	Treatment administered			
	Cetuximab monotherapy: Vermorken 2007[27] (N = 103)	Cetuximab+Cisplatin or carboplatin: Baselga 2002,2005[28,29] (N = 96)	Cetuximab+Cisplatin: Herbst 2005[30] and Kies 2002[31] (N = 79)	Various second-line treatments: Leon 2003,2005[6,7] (All treatments, N = 151; CT, N = 43)
Disease characteristics of recruited patients	Stage III/IV, recurrent and/or metastatic SCCHN, not suitable for local therapy, with documented PD; measurable disease	Histologically confirmed, stage III/IV SCCHN (AJCC), not suitable for local therapy, with documented PD; measurable disease	Pathologically confirmed, recurrent SCCHN; bidimensionally measurable disease; prior total cisplatin exposure $\leq$200 mg/m^2 at initiation of study or $\leq$450 mg/m^2 after an eligibility amendment	Histologically confirmed, stage III/IV, recurrent and/or metastatic SCCHN (AJCC), not suitable for local therapy, with documented PD; measurable disease
Other key inclusion criteria	Age $\geq$18 y; KPS $\geq$60%; tumor tissue available for defining EGFR expression by IHC	Age $\geq$18 y (19 y in Austria); KPS $\geq$60%; tumor tissue available for defining EGFR expression by IHC; adequate hematologic, renal, and hepatic function	Age $\geq$18 y; KPS $\geq$60%; tumor tissue available for defining EGFR expression by IHC; adequate hematologic, renal, and hepatic function	Age $\geq$18 y
Main exclusion criteria	NPC; concomitant malignant disease*; CT or RT within last 3 wk or prior platinum-containing CRT within 6 mo; prior or concomitant surgery within last 30 d; concurrent, chronic, systemic IT/CT for disease other than cancer or HT not indicated in protocol; previous exposure to HER/EGFR-targeted therapies	NPC; prior or concomitant surgery or RT within last 30 d or prior platinum-containing CRT within 6 months; concomitant malignant disease*	Prior murine MAb therapy or cetuximab therapy; previous therapy with an investigational agent within 1 mo of study entry; prior surgery or RT within 2 mo of study entry	NPC; prior treatment with experimental drugs not commercially available before 2001

CT indicates chemotherapy; SCCHN, squamous cell carcinoma of the head and neck; PD, progressive disease, AJCC, American Joint Committee on Cancer; KPS, Karnofsky performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; NPC, nasopharyngeal carcinoma; RT, radiotherapy; IT, immunotherapy; HT, hormone therapy; HER, human epidermal receptor; CRT, chemoradiotherapy; MAb, monoclonal antibody.

* Except adequately treated basal cell carcinoma of the skin or cervical cancer in situ.

TABLE 2
Criteria for Platinum Resistance*

Trial	Cetuximab monotherapy	Cetuximab+Cisplatin or carboplatin	Cetuximab+ Cisplatin	Various treatments
Time between last platinum dose and disease progression, d	<30	<30	After 2 cycles[†]	<30
Maximum no. of cycles of platinum therapy	2–6	2–4	2	2–4
Minimum doses of platinum: (mg/m2)				
Cisplatin	$\geq$60	$\geq$60	$\geq$75	$\geq$60
Carboplatin	$\geq$300[‡]	$\geq$250		$\geq$250

* See Vermorken 2005.[33]

† Of cisplatin-based chemotherapy (maximum dose 450 mg/m^2).

‡ Or an area under the concentration-time curve $\geq$4.

The analysis described here, which originally was presented at the Annual Meeting of the American Society of Clinical Oncology (2005), was conducted before the availability in the literature of full details for all studies. At the time this report was written, all of the studies had been published. In this current report, the most recent publications of the studies were used in addition to the original presentation to provide information on the designs, patient eligibility, and other relevant information. However, most of

the data are presented according to the original analysis: When data were derived from a different source, this is clearly indicated in the text.

Treatments Administered

The cetuximab monotherapy study had a 2-phase design.[27] First, patients received cetuximab monotherapy at an initial dose of 400 mg/m^2 followed by subsequent weekly 1-hour infusions of 250 mg/m^2 until PD. Patients who progressed on cetuximab monotherapy were offered salvage therapy with cetuximab plus platinum and entered a second combination-therapy phase of the study.

In the studies of cetuximab in combination with platinum, patients received cetuximab at the same schedule that was used in the monotherapy study, but this was followed by platinum chemotherapy either at the same dose and schedule at which PD had been documented before entry into the study[28,29] or at a dose of 75 mg/m^{2}or 100 mg/m^2 (cisplatin).[30,31] Patients received a minimum of 2 cycles[28,29] or 4 cycles[30,31] of therapy, at which point all patients with at least stable disease (SD) continued either until they developed PD or until the occurrence of unacceptable side effects with either the same combination regimen[28,29] or with cetuximab alone.[30,31]

In the retrospective study, 68 patients (45%) patients received BSC, 43 patients (28%) received chemotherapy, 25 patients (17%) received radiotherapy, and 15 patients (10%) received chemoradiotherapy. In total, therefore, 58 patients received second-line chemotherapy either alone (n = 43) or in combination with radiotherapy (n = 15). Of these 58 patients, 13 patients (22%) received single-agent chemotherapy, mostly methotrexate and gemcitabine, and 45 patients (78%) received combination chemotherapy (either platinum-based; combined methotrexate, cisplatin, and bleomycin; or taxane-based). Overall, 40 of 58 patients (69%) received some form of platinum-based chemotherapy. All drugs used were available commercially.

Endpoints

The primary endpoint in all the prospective studies was response to treatment, which was defined as the best confirmed response. Response was assessed by using modified World Health Organization (WHO) criteria and is described briefly as follows: a complete response (CR) was defined as the disappearance of all index lesions (or, for nonindex lesions, no new lesions); a partial response (PR) was defined as a reduction $\geq$50% in the sum of the products of the greatest dimensions (SOPD) of index lesions compared with baseline SOPD with no evidence of PD; SD was defined as no sufficient decrease or increase in index lesions to qualify for PR or PD, respectively; and PD was defined as an increase $\geq$25% in the SOPD of index lesions compared with the smallest SOPD recorded for the study period (global nadir SOPD) or the appearance of 1 or more new lesion(s) and/or unequivocal progression of existing nonindex lesions. PD status at study entry and subsequent tumor response were assessed independently by either a blinded review committee[26–29] or a radiologist.[30,31]

Secondary endpoints, which varied between the prospective studies, included overall survival, disease control rate (percentage of patients with CR, + PR + SD), time and duration of response, time to progression (TTP), quality of life, change in Karnofsky performance status (KPS) from baseline, and symptomatic changes. In the retrospective study,[6,7] only 83 of 151 patients (55%) could be evaluated for response, as because nearly half (45%) received only BSC; thus, a response could not be expected in these patients. Consequently, survival was the most reliable endpoint against which valid and clinically meaningful comparisons can be made.

Pretreatment and On-study Evaluations

Pretreatment screening procedures and on-study evaluation protocols have been described previously.[6,7,27–31] Within each of the prospective studies, adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2 and were described by using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (1995) dictionary. Safety was not analyzed in the retrospective study.[7]

Statistical Analyses

The findings reported here represent a descriptive analysis of data from 3 prospective studies and 1 retrospective study. These data were not subject to any formal statistical analysis.

Within individual studies, continuous variables were summarized by using descriptive statistics. Qualitative variables were summarized by using counts and percentages. Two-sided confidence intervals were calculated for response and disease control rates. Kaplan-Meier estimates were used for time-to-event endpoints.[32]

In the 3 prospective studies,[27–31] the primary population for efficacy and safety analyses was the intention-to-treat (ITT) population (defined as all patients enrolled into the study who received cetuximab). Safety analyses were conducted on the ITT population. Details of statistical analyses are provided in the individual study reports.

TABLE 3
Patient and Disease Characteristics at Baseline in the Prospective and Retrospective Studies*

Characteristic	Cetuximab therapy			
	Cetuximab monotherapy (N = 103)	Cetuximab+Cisplatin or carboplatin (N = 96)	Cetuximab+Cisplatin (N = 79)	Various treatments (N = 151)
Median/mean age, y	57	56	55	57.8
Median KPS, %	80	80	80	70†
Patients with metastatic disease, %	48	41	43	34
EGFR expression, %	94	98	100‡	NA
Median time since PD, d	15	15	NA	NA
Prior platinum therapy, %	100	100	100	100

KPS indicates Karnofsky performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; NA, not available.
* See Vermorken 2005.[33]
† Available for 123 patients.
‡ For 15 patients, no adequate tissue was available for EGFR determination.

TABLE 4
Response Rate, Disease Control Rate, Survival, and Time to Progression in Patients Who Received Cetuximab With or Without Platinum or a Variety of Second-line Treatments*

Treatment	No. of patients	Response rate (95% CI), %†	Disease control rate (95% CI), %‡	Median survival (95% CI), mo	Median TTP (95% CI), mo
Cetuximab monotherapy	103	13 (7–21)	46 (36–56)	5.9 (4.9–7.1)	2.3 (1.6–3.1)
Cetuximab+cisplatin or carboplatin	96	10 (5–18)	53 (43–63)	6.1 (4.9–7)	2.8 (2.2–3.8)
Cetuximab+cisplatin	79	10 (5–19)	56 (44–67)	5.2 (3.1–6)	2.2 (1.9–3)
Retrospective study					
All patients	151	3 (1–7)	15 (10–22)	3.4 (2.6–4.2)	NA
Patients with chemotherapy only	43	0 (0–8)	9 (3–22)	3.6 (2.7–4.4)	NA

95% CI indicates 95% confidence interval; TTP, time to progression; NA, not available.
* See Vermorken 2005.[33]
† Complete response (CR)+partial response (PR).
‡ CR+PR+stable disease.

RESULTS

The patient and disease characteristics were similar in the 3 prospective cetuximab studies and were typical of those expected in a population of patients with recurrent and/or metastatic SCCHN (Table 3). The median KPS was 80%, and tumor EGFR expression was detected in 94% to 100% of all tested patients. Patients in the retrospective study had patient and disease characteristic profiles similar to those in the prospective studies. The exception was the median KPS, which, at 70%, was lower in the retrospective study than in the prospective studies, although data were available for only 81% of patients.

Response to Treatment

In total, 278 patients with recurrent and/or metastatic SCCHN who progressed on platinum-based therapy subsequently were treated with either cetuximab alone (N = 103) or in combination with platinum (N = 175). The efficacy results of the 3 prospective studies with cetuximab are summarized in Table 4.[33] Response rates ranged between 10% and 13%, disease control rates ranged between 46% and 56%, and the median TTP ranged between 2.2 months and 2.8 months. The median survival in the cetuximab monotherapy study was 5.9 months compared with 6.1 months and 5.2 months in the cetuximab plus cisplatin/carboplatin and cetuximab plus cisplatin studies, respectively. Thus, the efficacy of cetuximab therapy clearly was superior to that of the various treatments used in the retrospective study, in which the median survival was 3.4 months (3.6 months in patients who received chemotherapy alone). Kaplan-Meier estimates of survival for all 4 studies are shown in Figure 1. In Figure 2, the survival curve for patients in the retrospective study

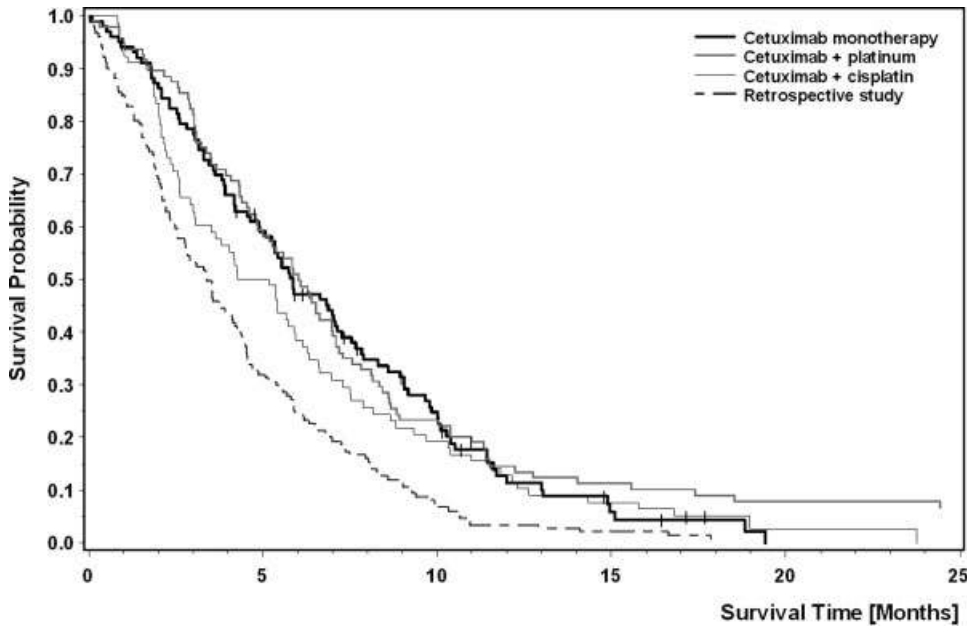

FIGURE 1. Kaplan-Meier overall survival estimates for patients with squamous cell carcinoma of the head and neck who failed on platinum-based therapy and received either cetuximab with or without platinum-based therapy or various second-line treatments.

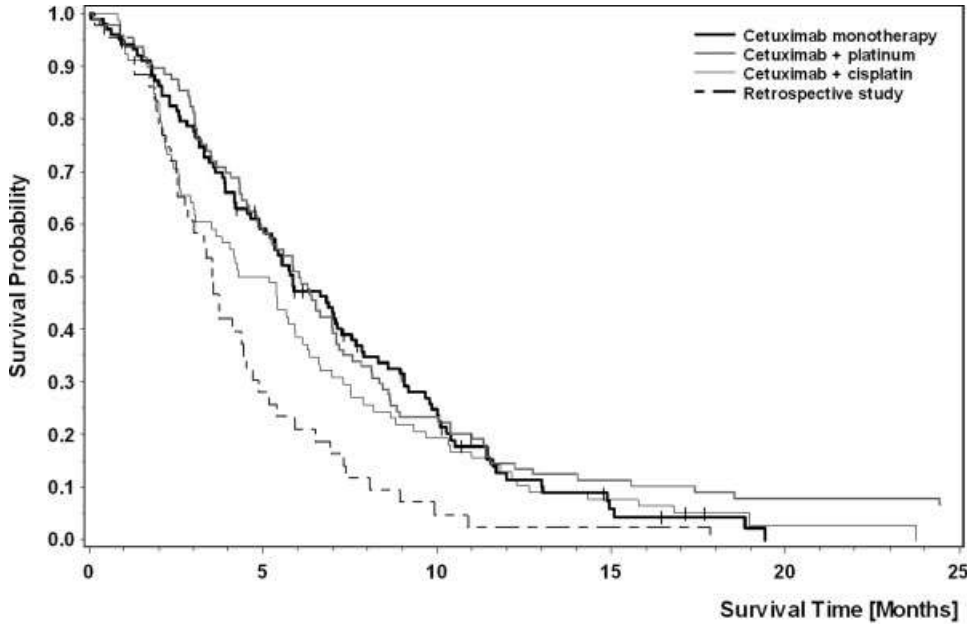

FIGURE 2. Kaplan-Meier overall survival estimates for patients with squamous cell carcinoma of the head and neck who failed on platinum-based therapy and received either cetuximab without or without platinum-based therapy or various chemotherapy regimens.

who received chemotherapy alone and, thus, may have been even more comparable to the prospective cetuximab studies, is presented along with the survival curves for patients in the 3 cetuximab studies.

It is noteworthy that there was no clear difference in the median TTP and survival between the 2 studies using cetuximab plus platinum therapy and the study that investigated cetuximab monotherapy (Fig. 3).[33] In the cetuximab monotherapy study, 53 patients who progressed on single-agent therapy went on to receive cetuximab in combination with platinum[27] in the second, combination phase of the

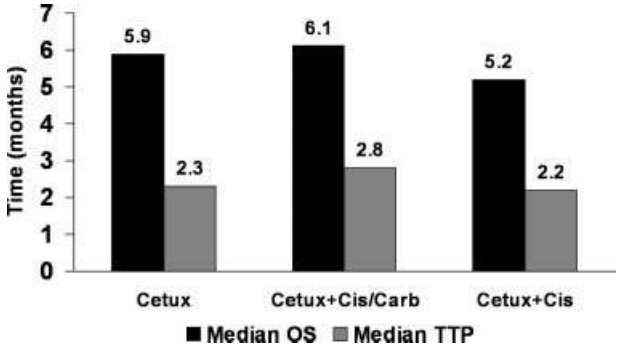

FIGURE 3. The addition of platinum to cetuximab offers no obvious survival benefit over cetuximab alone in patients with disease failing platinum therapy. Adapted from Vermorken 2005.[33] Cetux indicates cetuximab; Cis, cisplatin; Carb, carboplatin; OS, overall survival; TTP, time to progression.

study. None of these patients achieved a CR or PR. SD and PD were each reported in 26% of patients. In 47% of patients, however, responses were not evaluable.

Safety and Tolerability

Over all studies reported, cetuximab was tolerated well either as monotherapy or in combination with cisplatin or carboplatin. Relevant cetuximab-related grade 3/4 adverse events that were reported in the cetuximab studies are summarized in Table 5.[27,28,30] There was a low incidence of grade 3/4 side effects, which included fatigue, fever/chills, nausea and vomiting, acne-like rash, diarrhea, and infusion-related reactions. Acne-like rash is observed commonly with EGFR inhibitor use and generally is easy to manage.[34,35] In the 3 studies, there were only 9 reports (3%) of grade 3/4 rash. Infusion-related reactions are characteristic of treatment with monoclonal antibodies and generally occur with a low incidence with cetuximab. In the cetuximab monotherapy study, there was 1 treatment-related death because of an infusion-related reaction. No cetuximab-related deaths were reported in the 2 other cetuximab studies. Data from the cetuximab plus platinum studies suggested that cetuximab most likely did not increase the side effects associated with the use of platinum therapy.

The development and/or severity of acne-like rash has been identified as a predictor of response to treatment with cetuximab in a range of tumor types.[36] According to the published report from 1 of the studies in this analysis, there appeared to be a relation between skin reactions and response in patients who were receiving cetuximab plus cisplatin. A higher response rate was observed in patients who developed grade 1 (13%) or grade 2 and 3 (15%) skin reactions compared with patients who did not develop skin reactions (4%).[30]

TABLE 5
Grade 3/4 Adverse Events With Cetuximab Alone or in Combination With Platinum Therapy in the Treatment of Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Progressed on Platinum Therapy*

	No. of patients (%)		
Adverse Event	Cetuximab monotherapy: Vermorken 2007[27] (N = 103)	Cetuximab+ Cisplatin or carboplatin: Baselga 2005[28] (N = 96)	Cetuximab+ Cisplatin: Herbst 2005[30] (N = 131)
Acne-like rash	1 (1)†	3 (3)	5 (4)‡
Fatigue/asthenia/malaise	4 (4)	18 (19)	22 (17)
Fever/chills	1 (1)	3 (3)	NR
Nail changes	0 (0)	NR	1 (1)
Nausea/vomiting	3 (3)	6 (6)	10 (8)
Infusion-related reactions	1 (1)§	0 (0)	7 (5)
Dyspnea	4 (4)	NR	NR

NR indicates not reported.
* Adverse event categories are based on those defined in the cetuximab monotherapy presentation as 'cetuximab-related adverse events' (see Vermorken 2007[27]).
† Includes rash and acne.
‡ Includes all categories of rash.
§ One treatment-related death was caused by an infusion-related reaction.

DISCUSSION

Until relatively recently, there was little evidence to support the use of second-line chemotherapy in patients with recurrent and/or metastatic SCCHN.[37,38] Patients who have progressed on cisplatin-containing therapy not only have exhausted the most active, current, first-line treatment, they also often are a, or near their limit of chemotherapy tolerability. Consequently, no regimen has been approved to date for use in patients with recurrent and/or metastatic SCCHN who fail on platinum-based therapy. Although experimental second-line chemotherapy with third-generation cytotoxic agents (vinorelbine, docetaxel, or paclitaxel given alone or in combination) has been investigated in several small studies, it has not been possible to draw definitive conclusions on their clinical benefit.[8,9,39,40] The dismal outlook for patients with PD was confirmed by the retrospective study that was included in this analysis, which showed a median survival of only 3.6 months for patients who received chemotherapy.[6,7]

The objective of this analysis was to view, within the limitations of a comparison with retrospectively gathered data, the results of cetuximab treatment in the context of what can be expected with commonly

used treatment approaches in the clinical setting. The 4 studies in the analysis generally were matched well in terms of patient and disease characteristics. In the 3 cetuximab studies, the use of an independent review committee or radiologist to confirm disease progression before treatment ensured the selection of patients who had disease that no longer responded to platinum therapy.

Response rates and disease control rates across the 3 cetuximab studies were consistent (10%–13% and 46%–56%, respectively), and the robustness of these results was underscored by the independent assessment of response data. Meaningful comparison of response data between the cetuximab studies and the retrospective study was precluded by the absence of response criteria for the retrospective study. A more representative comparison of the different treatments can be achieved by comparing survival data. The median survival of 5.9 months in the cetuximab monotherapy study was outstanding in this disease setting and represents an increase in median survival of 2.5 months over patients in the retrospective study who were receiving a variety of second-line treatments. Of the 151 patients in the retrospective study, 45% received BSC, reflecting a possibly less favorable physical condition but, conversely, underscoring the lack of established therapeutic options in this setting. When the results from the cetuximab monotherapy study were compared with the more closely matched subset of patients in the retrospective study (who received chemotherapy only), there still was a clinically significant increase of 2.3 months in survival. The cetuximab monotherapy data also indicated a survival benefit of 1.4 months compared with published data from a small Phase II study with vinorelbine, bleomycin, and methotrexate as second-line treatment (5.9 months vs 4.5 months).[9] Although the current analysis was based on information that was available before the publication of full details for all studies that we included, the data are consistent with those reported in the subsequently published reports, confirming the findings of the analysis.

The median survival achieved with cetuximab monotherapy was similar to that reported with cetuximab in combination with platinum therapy (6.1 months and 5.2 months, respectively),[33] suggesting that there is no obvious benefit of a combined use of platinum plus cetuximab over cetuximab alone in patients who fail on platinum-based therapy. The usefulness of cetuximab in patients with recurrent and/or metastatic SCCHN who progress on platinum therapy, based on efficacy findings, is supported by its safety profile. There were no unexpected side effects, and the profile of grade 3/4 cetuximab-related adverse events in the cetuximab monotherapy study was in keeping with what has been reported for cetuximab in colorectal cancer.[41] In addition, adding cetuximab to platinum therapy did not increase the expected side effects. Skin reactions, particularly an acne-like rash, are observed commonly with EGFR inhibitors, including both monoclonal antibodies and tyrosine kinase inhibitors, and generally are easy to manage.[35] Skin reactions have been suggested as a potential predictive marker for response to cetuximab, and data from 1 of the studies in the current analysis (combining cetuximab and cisplatin) confirmed this.[30] However, because we know that patients who do not develop a rash also can respond to cetuximab, the utility of skin reactions as a predictive marker requires further investigation.

In conclusion, this analysis demonstrated that cetuximab is effective as monotherapy in patients with recurrent and/or metastatic SCCHN who progress on platinum-based therapy and is associated with a clinically meaningful increase in survival of 2.5 months compared with a retrospective study of patients who received a variety of second-line therapies. On the basis of the analysis presented, and recognizing the limitations of comparison with a retrospective study, cetuximab monotherapy can be considered a real therapeutic option for these patients with a poor prognosis.

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