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ORIGINAL REPORT

Phase II Study of Cetuximab As First-Line Single-Drug Therapy in Patients With Unresectable Squamous Cell Carcinoma of the Skin

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ABSTRACT

Purpose
To evaluate the efficacy and safety of cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR), as a first-line monotherapy in patients with unresectable squamous cell carcinoma of the skin (SCCS).

Patients and Methods
Thirty-six patients received cetuximab (initial dose of 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2) for at least 6 weeks with a 48-week follow-up. The primary end point was the disease control rate (DCR) at 6 weeks (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria). Secondary end points included best response rate, overall survival, progression-free survival (PFS), and toxicity assessment. Association of treatment efficacy with *RAS* mutations or FcγR genotypes was investigated.

Results
Median age of the study population was 79 years. DCR at 6 weeks was obtained in 25 of 36 patients (69%; 95% CI, 52% to 84%) of the intention-to-treat population. The best responses were eight partial responses and two complete responses. There were no cetuximab-related deaths. There were three related serious adverse events: two grade 4 infusion reactions and one grade 3 interstitial pneumopathy. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS. One *HRAS* mutation was identified. Combined FcγRIIa-131H/H and/or FcγRIIIa-158V/V polymorphisms were not associated with the clinical outcomes.

Conclusion
As a first-line treatment in patients with unresectable SCCS, cetuximab achieved 69% DCR. A randomized phase III trial is warranted to confirm that cetuximab may be considered as a therapeutic option especially in elderly patients. The low frequency of *RAS* mutations in SCCS makes SCCS tumors attractive for EGFR inhibition.

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INTRODUCTION

Approximately 20% to 30% of nonmelanoma skin cancers are squamous cell carcinomas of the skin (SCCS). The incidence of SCCS has increased over time, and there are now 200,000 to 300,000 new cases per year in the United States. SCCS often occur in elderly or immunosuppressed patients. In France, the incidence is estimated to be at least 30 per 100,000 persons per year, and the mean age at diagnosis of SCCS is 74 years in males and 77 years in females.[1] Most patients with primary SCCS have an excellent prognosis, but SCCS can progress to advanced stages that are impossible to treat by surgical excision or radiotherapy.[2] Few therapeutic options are available for these tumors. Conventional chemotherapy, such as cisplatin-based combinations, has some efficacy, but the toxic effects of these combinations often prohibit their use in elderly patients.[3]

The epidermal growth factor receptor (EGFR) is highly expressed in many epithelial tumors, including squamous cell carcinoma of the head and neck (SCCHN) and SCCS.[4-7] This glycoprotein plays a crucial role in signal-transduction pathways that regulate key cellular functions.

Cetuximab is a monoclonal antibody that competitively inhibits EGFR. It has been approved for the treatment of SCCHN and colorectal carcinoma

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(CRC). In an open-label, uncontrolled, phase II study of patients with advanced SCCHN who had progressed on platinum therapy, the response to single-drug cetuximab was comparable with the response to cetuximab plus platinum combination regimens.[8-10] Concerning SCCS, no prospective trial has been performed, and only a few retrospective case reports have described the effects of cetuximab. Among nine patients treated with cetuximab, seven exhibited a response,[11-17] and we hypothesized that cetuximab may be effective as a single agent in the first-line treatment of patients with unresectable SCCS.

We therefore aimed to determine the efficacy and safety of single-agent cetuximab in patients with chemotherapy-naive unresectable SCCS. A 6-week disease control rate (DCR) primary end point was selected to mimic the evaluation schedule performed after two cycles at 6 weeks in patients with advanced SCCS treated with cisplatin-based chemotherapy and to avoid a loss of opportunity to treat in the case of early disease progression. We also studied efficacy as a function of skin toxicity as documented in SCCHN after cetuximab treatment.[9]

Since cetuximab sensitivity is related to KRAS status in CRC, we also investigated the effects of several biologic parameters, including *BRAF/HRAS/KRAS/NRAS* mutations status and combined FcγRIIa-131H/H and/or FcγRIIIa-158V/V polymorphisms on the outcome of patients with SCCS treated with cetuximab.[18-22]

PATIENTS AND METHODS

Study Design and Objectives

The trial was an open-label, uncontrolled, multicenter phase II study that was conducted in 10 French centers. The primary end point was to assess the DCR (complete response [CR], partial response [PR], or stable disease) after 6 weeks of treatment with cetuximab.

Secondary end points were response rate (RR = CR or PR) after 6 weeks of treatment with cetuximab; best overall study DCR and disease response rate; overall survival (OS) calculated as the number of days from the first infusion of cetuximab until week 48 or death; progression-free survival (PFS) defined as the number of days from the first dose of cetuximab to the earliest day of either progression or starting another anticancer treatment, or death; duration of control among patients whose disease was controlled at week 6 calculated as the number of days from the start of treatment to the earliest day of progressive disease without other anticancer treatment; duration of response defined similarly as duration of control but estimated in patients with response any time during the study; and safety profile, including occurrence of acne-like rash.

Patient Eligibility

Eligibility requirements included pathologically confirmed SCCS as well as immunohistochemical evidence of strong or moderate EGFR expression, locally advanced SCCS that was surgically unresectable, or metastatic SCCS, with documented progression. Patients had to be chemotherapy-naive. Other eligibility criteria included age $\geq$ 18 years; Eastern Cooperative Oncology Group performance status $\leq$ 2; life expectancy $\geq$ 3 months; presence of at least one measurable target lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria; at least one accessible lesion for biopsies; and adequate hematologic, hepatic, and renal functions. Exclusion criteria included prior radiotherapy within the last 4 weeks, prior therapy with an agent that targets EGFR, unstable systemic diseases, or active uncontrolled infections.

The study protocol and any amendments were approved by an independent ethics committee. All patients signed written informed consent.

Study Treatment

Cetuximab was administered as an intravenous infusion at an initial dose of 400 mg/m^2, followed by weekly 1-hour infusions of 250 mg/m^2. Patients received pretreatment with an antihistamine. As specified in the summary of product characteristics of cetuximab, in case of infusion reactions or dermatologic toxicity, dose modifications were planned. Cetuximab could be continued as long as the response or the stabilization persisted, even beyond 48 weeks, which was the end of the per-protocol study.

Assessment

All patients underwent pretreatment screening during the 4 weeks before starting the study, including full medical history, physical examination, biologic assessments, and determination of tumor EGFR status, as previously described, by using immunochemistry performed by an independent pathologist.[7] Initial disease staging was performed by using computed tomography (CT) or magnetic resonance imaging scans of target lesions, and chest, abdomen, and pelvis. The aim was to include 28 evaluable patients (ie, patients who were to receive cetuximab for at least 6 weeks) and perform follow-up for 48 weeks after starting treatment. Tumor response was assessed according to RECIST criteria every 6 weeks until progression.[23] CR and PR required confirmation after a minimum of 4 weeks. An independent radiologist (P.P.) verified response status during treatment. Response to cetuximab was also evaluated retrospectively by two other independent radiologists (Caroline Malhaire and Alexandra Athanasiou). All three radiologists were blinded to clinical outcomes. In cases of discordance between the three radiologists, the evaluation was reviewed by a committee (P.P., Caroline Malhaire, Alexandra Athanasiou, and Liliane Ollivier) and eventually reassessed by the radiologists together until a consensus was obtained. This final evaluation was taken into account for the analysis.

Toxicity was evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). All serious adverse events (SAEs) were reviewed by a data safety monitoring board every 2 months. All patients assessed with progressive disease were followed for survival every 12 weeks until week 48 or death.

Biologic Studies

DNA was extracted from the 28 pretreatment tumor biopsies remaining after the immunochemistry evaluation of EGFR expression. All coding sequences of exon 15 of *BRAF* (NM_004333.4), exon 2 and 3 of *KRAS* (NM_033360.2), *NRAS* (NM_002524.3), *HRAS* (NM_005343.2), exon 4 of *FCGR2A* (NM_001136219), and *FCGR3A* (NM_000569.6) were analyzed in at least two independent experiments. Sanger direct sequencing was performed after polymerase chain reaction amplification of targeted exons and use of the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA). Primer sequences are available on request. Sequencing reactions were analyzed on a 48-capillary 3730 DNA Analyzer (Applied Biosystems). Reading and alignment of sequences were performed with SeqScape software (Applied Biosystems). Sequence analyses for *FCGR2A* were focused on polymorphism rs1801274 (known as FcγRIIa-131H/R) and for *FCGR3A* and polymorphism rs396991 (known as FcγRIIIa-158V/F) to determine tumor genotype.

Statistical Analyses

Statistical analyses were carried out on the intention-to-treat (ITT) population (ie, all included patients in whom missing evaluation was defined as failure) and the per-protocol (PP) population (ie, patients treated for at least 6 weeks and radiologically evaluable for tumor response). It was planned to include at least 28 patients to show that DCR at week 6 was significantly greater than 15% (by using a two-sided binomial test with type I error 5%, power 80%) and assuming that DCR with cetuximab treatment would be 40% in the ITT population. Two-sided exact 95% CIs for DCR and CR were calculated. OS, PFS, duration of control, and duration of response were estimated by using Kaplan-Meier survival analyses. Associations between efficacy outcomes and biologic features (*KRAS* and *BRAF* mutations and FcγRIIa and FcγRIIIa polymorphisms separately or both combined) were tested in the PP population by using Fisher's exact test for rates and log-rank test for durations. Associations between efficacy outcomes and occurrence of acne-like rash were similarly tested in the PP population. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

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Table 1. Patient Characteristics at Study Entry (N = 36)

Characteristics	No. of Patients	%
Sex		
Male	21	58
Female	15	42
Age, years		
Median	79	
Range	32-95	
> 70	23	64
ECOG PS		
0	11	31
1	17	47
2	8	22
Primary tumor location		
Head and neck	5	14
Extremities	14	39
Trunk	17	47
AJCC disease stage		
Local disease	17	47
Lymph node disease	16	44
Distant metastases	3	8
Previous therapy		
Radiotherapy alone	2	6
Surgery alone	12	33
Radiotherapy and surgery	7	19
None	15	42
EGFR expression by IHC		
Moderate	10	28
Strong	26	72

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; PS, performance status.

RESULTS

A total of 36 patients were enrolled in the study between October 2005 and April 2008. Five patients were not evaluable for tumor response for the following reasons: two grade 4 infusion-related reactions occurred at the first cetuximab infusion preventing further administration; two patients could not be assessed at week 6 (rapid deterioration not allowing CT to be performed in one case, lymph node targets lesions not available on CT acquisitions in the other case), and there was one early death. Thus, 31 patients (86%) were included in the PP population.

Patient Characteristics

Patient characteristics are listed in Table 1. There was a predominance of males, and the median age of the population was 79 years (range, 32 to 95 years). Eighty-six percent of tumors were located on the trunk or extremities. Forty-seven percent of patients had an unresectable local disease, 44% had regional lymph node involvement, and 8% had distant metastases. Fifty-eight percent of patients had either prior surgery or radiotherapy or both. High expression of EGFR in SCCS was observed in 72% of patients. No patients with underlying hematologic malignancy or other causes of immunosuppression were enrolled in the study.

Exposure to Cetuximab

The median number of cetuximab infusions administered during the 48-week trial was 15 (range, 1 to 47 infusions). Three patients (8%) received only one infusion; 21 patients (58%) received between six and 18 infusions, and 12 patients (33%) received more than 18 infusions. Only one patient was still receiving the study drug at week 48 and ultimately received cetuximab for 21 months. Grade 3 to 4 cetuximab-related adverse events (AEs) led to discontinuation of cetuximab in four patients but no infusions were postponed and no dose reduction was required.

Response and Disease Control Rates

At week 6, the DCR was 69% (95% CI, 52% to 84%) in the ITT population and 81% (95% CI, 63% to 93%) in the PP population (Table 2). Both rates were significantly higher than 15% ($P < 10^{-12}$ and $P < 10^{-14}$, respectively). The RR was 11% (95% CI, 3% to 26%) at week 6 in the ITT population. One patient achieved a CR at week 6. The best overall study DCR was similar to the DCR at week 6 and the best overall RR was 28% (95% CI, 14% to 45%). This included six patients with initial local disease, three patients with initial regional disease, and one patient with initial distant disease. Two patients achieved a CR, one of whom had regional lymph node involvement. One of these responses was confirmed by pathologic examination (Fig 1A). These two CRs were maintained 2.5 years after stopping treatment. Furthermore, two patients with locally advanced T3 and T4 tumors and one TxN1M0 patient who

Table 2. Response and Disease Control Rates

	Response at Week 6						Best Overall Response					
	ITT Population (n = 36)			PP Population (n = 31)			ITT Population (n = 36)			PP Population (n = 31)		
Variable	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
Complete response	1	3		1	3		2	6		2	6	
Partial response	3	8		3	10		8	22		8	26	
Stable disease	21	58		21	68		15	42		15	48	
Progressive disease	6	17		6	19		6	17		6	19	
Not assessable	5	14		0	0		5	14		0	0	
Response rate		11	3 to 26		13	4 to 30		28	14 to 45		32	17 to 51
Control rate		69	52 to 84		81	63 to 93		69	52 to 84		81	63 to 93

Abbreviations: ITT, intention-to-treat; PP, per-protocol.

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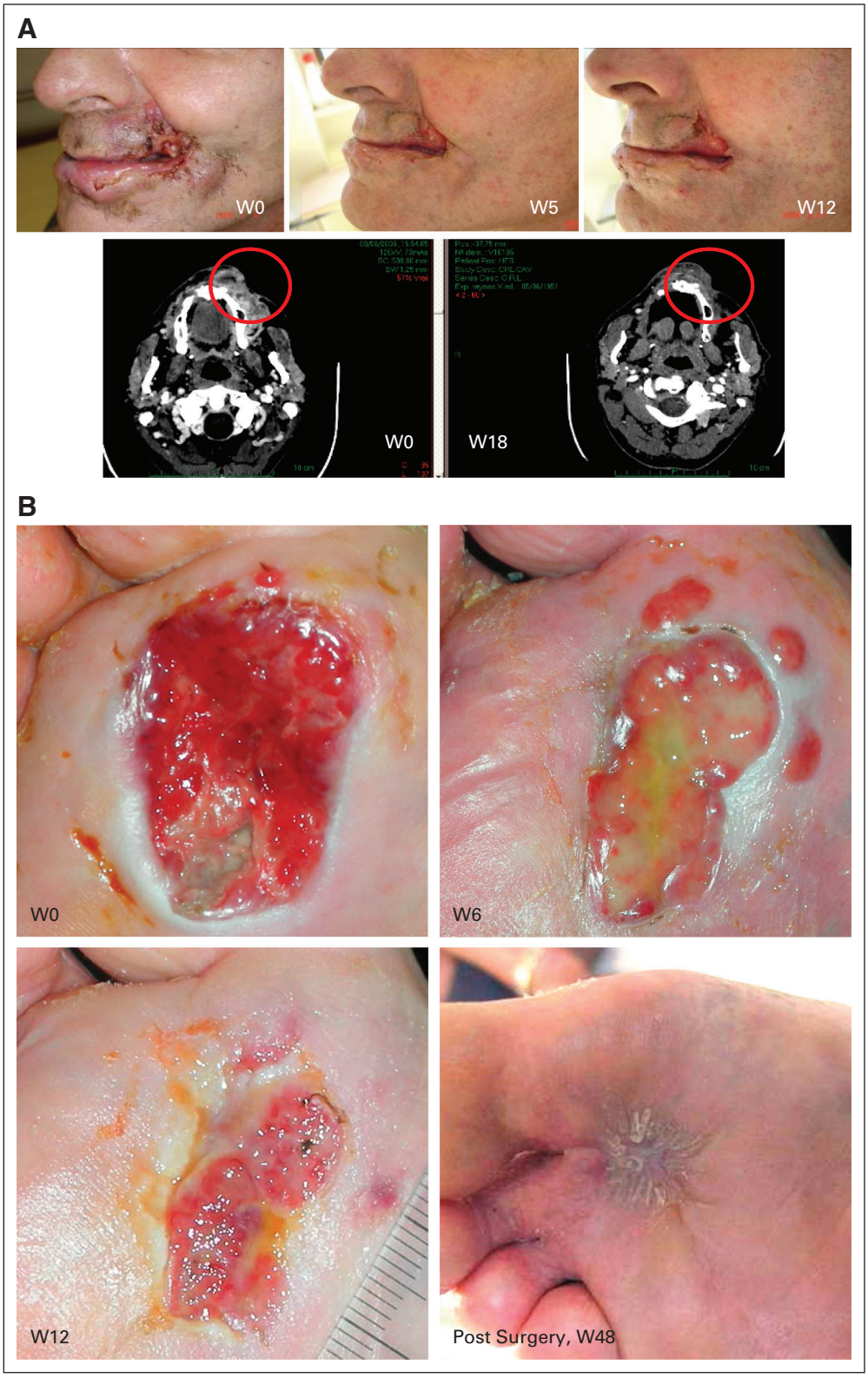

Fig 1. Representative examples of patients showing response to cetuximab. (A) A 55-year-old male with a local T3 tumor experienced a partial response at week 18. Surgery could be performed at week 24, and histologic examination was tumor free. He was evaluated as a complete responder. He has remained free of disease 2.5 years later. (B) A 64-year-old male with a T4 tumor was initially proposed a partial amputation of the foot before inclusion in the study. He presented a partial response at week 12 and underwent a conservative surgical excision of the primary tumor after treatment with cetuximab. He has remained free of disease 3 years later.

had presented partial or minor responses underwent a conservative surgical excision of the primary tumor and lymph node dissection after treatment with cetuximab. Histopathologic examination showed residual disease in these three patients. Among these three patients who underwent a complementary surgical excision, one remains disease-free 3 years after surgery (Fig 1B), whereas the two other patients developed a local or regional relapse 7 months and 2 years, respectively, after surgery.

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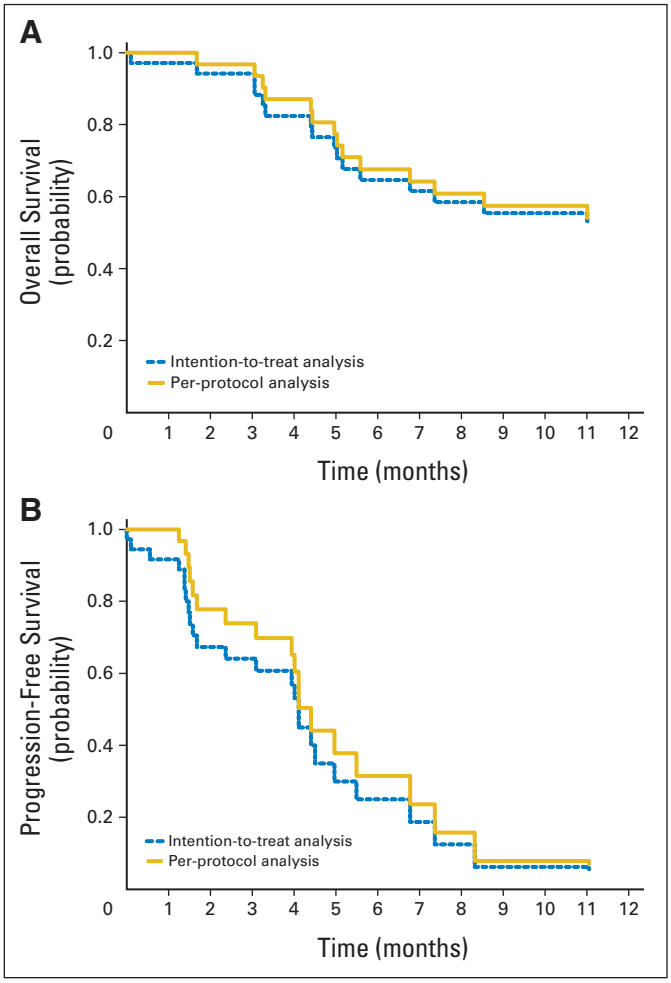

Fig 2. Kaplan-Meier plot of (A) overall survival and (B) progression-free survival in the intention-to-treat population and per-protocol population.

Table 3. Most Common or Relevant Cetuximab-Related Adverse Event Categories by NCI CTC Toxicity Grade in the ITT Population (N = 36)

Adverse Event Category	All Grades		Grade 3 to 4	
	No. of Patients	%	No. of Patients	%
Any category	36	100	23	64
Acne-like rash	28	78	0	0
Infection	13	36	8	22
Dry skin/pruritis*	12	33	1	3
Nausea/vomiting	10	28	1	3
Eye disorder†	10	28	0	0
Nail/hand disorder	10	28	0	0
Asthenia	9	25	0	0
Fever	8	22	0	0
Tumor bleeding	5	14	4	11
Diarrhea	4	11	0	0
Infusion-related reactions	3	8	2	6
Pilosity disorder	3	8	0	0
Headache	2	6	0	0
Interstitial pneumonitis	1	3	1	3

Abbreviations: ITT, intention-to-treat; NCI CTC, National Cancer Institute Common Toxicity Criteria.
*The item "Dry skin/pruritis" also includes the grade 3 adverse event: worsening of skin conditions of a recessive epidermolysis bullosa.
†The item "Eye disorder" includes cases of blepharitis, conjunctivitis, ectropion, and eye dryness.

OS, PFS, and Control and Response Durations

In the ITT population, the mean OS was 8.1 months (95% CI, 6.9 to 9.3 months), and the estimated proportion of patients alive at week 48 was 52% (95% CI, 34% to 68%; Fig 2A). The median PFS was 4.1 months (95% CI, 1.7 to 5 months; Fig 2B).

For the 25 controlled patients at week 6, the median duration of control was 5 months (95% CI, 4.1 to 7.4 months). Cetuximab provided a long-term control of the disease in two patients: more than 1 year for a patient with a T3 tumor and 8 months for a partial responder with lung metastasis. Overall, the median duration of response for the 10 patients who achieved a CR or PR was 6.8 months (95% CI, 4.1 to 8.3 months).

Safety and Tolerability

AEs were reported for all 36 patients. Major AEs are listed in Table 3. All these AEs were consistent with those previously reported in clinical trials that used cetuximab.

Seven patients died during treatment or within 30 days after the final administration. Three deaths were directly or indirectly related to disease progression, and four deaths—all in elderly patients (age ≥ 74 years)—were considered to be related to intercurrent events or general conditions.

The most frequent AE was an acne-like rash. Eighty-seven percent of the PP population (27 of 31) had grade 1 to 2 acne-like rash. However, no patients developed a grade 3 rash. The median time to the appearance of cetuximab-related acne-like rash was 14 days (range, 0 to 107 days).

Grade 3 or 4 SAEs were reported in 61% of patients. Of the 29 SAEs, 62% were considered to be unrelated to cetuximab, 28% were not assessable, and 10% were related to cetuximab. Four patients discontinued cetuximab. Of these, two had grade 4 cetuximab-related hypersensitivity reactions during the first infusion (these patients did not receive premedication with corticoids), one patient had grade 3 cetuximab-related bilateral interstitial syndrome, and the other patient presented a grade 3 worsening of recessive epidermolysis bullosa skin lesions. The other patients with grade 3 or 4 cetuximab-related SAEs were handled by treating their symptoms and could continue cetuximab without dose reduction.

There was a high incidence of infections but no infectious events were judged to be treatment related. The high frequency of infections (36%) was probably age-related; 69% of all infections and 83% of grade 3 to 4 infections occurred in patients older than 70 years. Moreover, these infections included seven skin infections in patients with ulcerated tumors or chronic dermatosis.

Acne-Like Rash and Efficacy

In the PP population, there was no significant association between occurrence of rash of any grade and DCR at week 6 (75% *v* 81%; $P = 1.00$) or best RR (0% *v* 37%; $P = .28$). However, for patients who developed an acne-like rash during treatment compared with those who did not, there was a significantly prolonged median PFS (4.5 *v* 1.7 months; $P = .004$) and a tendency for an improved mean OS (8.9 *v* 4 months; $P = .054$).

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Table 4. *BRAF, HRAS, KRAS,* and *NRAS* Status and Distribution of FcγR Polymorphisms

Characteristic	No.	% (among assessable patients)
BRAF exon 15 status		
Wild type	23	100
Nonassessable	5	—
HRAS exon 2 status		
Wild type	28	100
Nonassessable	0	—
HRAS exon 3 status		
Wild type	26	96
Mutated	1	4
Nonassessable	1	—
KRAS exon 2 status		
Wild type	28	100
Nonassessable	0	—
KRAS exon 3 status		
Wild type	25	100
Nonassessable	3	—
NRAS exon 2 status		
Wild type	26	100
Nonassessable	2	—
NRAS exon 3 status		
Wild type	20	100
Nonassessable	8	—
FcγRIIa 131 polymorphism		
H/H	9	39
H/R	11	48
R/R	3	13
Nonassessable	5	—
FcγRIIIa 158 polymorphism		
F/F	1	4
F/V	15	58
V/V	10	38
Nonassessable	2	—
FcγR combined polymorphism		
H/H and/or V/V	14	58
R and F	10	42
Nonassessable	4	—

Abbreviations: F, phenylalanine allele; FcγR, fragment c gamma receptor; H, histidine allele; R, arginine allele; V, valine allele.

Exploratory Studies

Exploratory studies were performed on 28 patients. Among the 28 samples, some were not amplifiable because of the poor quality of extracted DNA. No *BRAF/KRAS/NRAS* mutations were identified in the assessable patients (0%; 95% CI, 0% to 15%; Table 4). One activating mutation of the *HRAS* gene (p.Gln61Lys or Q61K) was found in a nonresponder patient. Table 4 shows the distribution of FcγR polymorphisms assessed on tumor DNA. There was no significant difference in DCR at week 6 (86% *v* 89%), best RR (43% *v* 11%), median PFS (5.5 *v* 3.6 months), or mean OS (6.5 *v* 5.4 months) between patients with FcγRIIa-131H/H and FcγIIIa-158V/V tumor genotypes.

DISCUSSION

In our study, first-line treatment with single-agent cetuximab showed a valuable clinical activity with an overall 69% DCR and 28% RR in patients with unresectable SCCS. Half the responders showed late responses occurring between week 6 and 18. As previously reported for cetuximab treatment of other tumors, a few patients were long responders or showed prolonged stabilization.

Although cross-study comparisons should be interpreted with care, this trial may be compared with the trial by Shin et al,[24] which included 39 patients with advanced SCCS treated by cisplatin chemotherapy, interferon alfa, and retinoic acid. The RR (28% in our study *v* 34% in the Shin et al study) and 1-year survival rates (52% *v* 58%, respectively) were similar. Our study population was characterized by advanced age, as is usually observed in patients with SCCS. However, our patients were far older (median age, 79 years; range, 32 to 95 years) than patients in the Shin study (median age, 64 years; range, 38 to 77 years) and in previously published series with conventional chemotherapy.[3,25] In an interim analysis of a phase II study that used gefitinib, Glisson et al[26] observed only a 15% RR and a 45% DCR among 20 evaluable patients with metastatic/recurrent SCCS.

The safety profile of the study treatment was acceptable and similar to that of other studies. Development of an acne-like rash is frequently associated with cetuximab. In this analysis, patients developing rash at any time during the study had 2.6 times longer median PFS than patients with no rash, confirming that skin rash might be a clinical marker of response, as reported in other studies.[27-29]

Among the patients with SCCS who were screened for expression of EGFR, only one tumor did not express EGFR and the patient was not included in the study. However, consistent with other reports,[27,30,31] tumor EGFR expression levels were not associated with treatment efficacy. Molecular markers could help select patients most likely to respond to cetuximab therapy. The *HRAS* gene is mutated in 9% of patients with SCCS.[32] However, as in other studies, we found no mutations in *KRAS, NRAS,* or *BRAF*.[32-35] The lack of *RAS* mutations, as observed in SCCHNs, makes SCCS tumors attractive for EGFR inhibition by cetuximab.[36] The *HRAS* (Q61K) mutation, which is a hotspot-activating mutation with oncogenic potential, has been reported mainly in thyroid tumors and in a few cases of skin cancers (two melanomas[37,38] and one keratoacanthoma[39]).

FcγRIIa and FcγRIIIa polymorphisms are independently associated with PFS in metastatic CRC.[21] For head and neck tumors, in vitro data showed that effector cells expressing the FcγRIIIa-158V/V allele were more effective in mediating lysis of SCCHN cells than those expressing FcγRIIIa-V/F and F/F alleles.[40] In our series, we could not confirm the prognostic value of these polymorphisms, and the findings of Bibeau et al[21] still have to be confirmed in a larger series. Some other molecular determinants of response may be implicated. Indeed, *EGFR* amplification and cytoplasmic expression of *PTEN* and *p53* mutations seem to predict cetuximab sensitivity in patients without *KRAS* mutation in patients with metastatic CRC.[41,42]

In conclusion, to the best of our knowledge, this is the first cetuximab prospective trial in patients with unresectable SCCS, and it showed the efficacy of single-agent cetuximab as a first-line treatment. A randomized phase III trial is warranted to confirm that cetuximab may be considered as a therapeutic option in this setting, particularly for elderly patients in whom chemotherapy is not appropriate.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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