Phase II Trial of ZD1839 in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

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Purpose: **The epidermal growth factor receptor (EGFR) is a mediator of squamous cell carcinoma of the head and neck (SCCHN) development. ZD1839 is an orally active, selective EGFR tyrosine kinase inhibitor. This phase II study sought to explore the activity, toxicity, and pharmacodynamics of ZD1839 in SCCHN.**

Patients and Methods: **Patients with recurrent or metastatic SCCHN were enrolled through the University of Chicago Phase II Consortium. Patients were allowed no more than one prior therapy for recurrent or metastatic disease and were treated with single-agent ZD1839 500 mg/d. Patient tumor biopsies were obtained and stained immunohistochemically for EGFR, extracellular signal-regulated kinase 1 (ERK1), and phosphorylated ERK1 (p-ERK). Study end points included response rate, time to progression, median survival, and inhibition of p-ERK.**

Results: **Fifty-two patients were enrolled (40 male and 12 female) with a median age of 59 years (range, 34 to 84 years). Fourteen patients received ZD1839 through a feeding tube. Half the cohort received ZD1839 as second-line therapy. Forty-seven patients were assessable for response, with an observed response rate of 10.6% and a disease control rate of 53%. Median time to progression and survival were 3.4 and 8.1 months, respectively. The only grade 3 toxicity encountered was diarrhea in three patients. Performance status and development of skin toxicity were found to be strong predictors of response, progression, and survival. Ten biopsy samples were assessable and revealed no significant change in EGFR or p-ERK expression with ZD1839 therapy.**

Conclusion: **ZD1839 has single-agent activity and is well tolerated in refractory SCCHN. In contrast to other reports, development of skin toxicity was a statistically significant predictor of response and improved outcome.**

J Clin Oncol 21:1980-1987. *© 2003 by American Society of Clinical Oncology.*

SQUAMOUS CELL carcinoma of the head and neck (SCCHN) often presents as a locally advanced disease; however, more than 50% of patients will eventually develop incurable local or metastatic disease. For these patients, therapeutic options are often palliative, while systemic chemotherapy has yet to demonstrate a substantial improvement in survival and produces considerable toxicity. Phase III randomized trials in patients with recurrent or metastatic SCCHN have demonstrated single-agent response rates between 10% and 15% and median survivals of 6 to 8 months, even with the use of combination chemotherapy.[1-6]

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Submitted October 7, 2002; accepted February 26, 2003.

Supported in whole or in part by Federal funds from the National Cancer Institute, National Institutes of Health, Bethesda, MD, under Contract No. N01-CM-17102; the University of Chicago Cancer Research Center, Chicago, IL (grant no. P30 CA14599); and a private donation from The Francis Lederer Foundation, Chicago, IL.

Presented in part at the Second International Chicago Symposium on Cancers of the Chest, Head, and Neck, Chicago, IL, October 4-6, 2001, and the Annual Meeting of the American Society of Clinical Oncology, May 18-21, 2002.

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0732-183X/03/2110-1980/$20.00

Since the first description of the epidermal growth factor receptor (EGFR) in 1980,[7] interest has grown in targeting this protein in cancer therapy. Expression of EGFR has been linked to carcinogenesis, metastasis, and survival in SCCHN patients.[8] Phosphorylation of EGFR cytoplasmic tyrosine residues initiates a cascade of signals that includes activation of the mitogen-activated protein kinase pathway.[8] The mitogen-activated protein kinase pathway culminates in activation and nuclear translocation of the extracellular signal-regulated kinase (ERK) 1 and 2 and transcription of its target genes.[9] Preclinical studies have confirmed that interruption of EGFR phosphorylation can inhibit these downstream activation events, lead to cell cycle arrest, and compromise tumor growth.[10-12]

ZD1839 (gefitinib) is an oral, low-molecular-weight anilinoquinazoline that reversibly inhibits EGFR tyrosine kinase activity. It has demonstrated an acceptable toxicity profile in phase I trials with predictable pharmacokinetics that established dose, schedule, and dose-limiting toxicity.[13]

This phase II trial was undertaken to assess the activity and tolerability of ZD1839 in recurrent or metastatic SCCHN given either orally or via gastrostomy tube at a fixed dose of 500 mg/d. In addition, this study sought to delineate the pharmacodynamics of ZD1839 in tumor tissue before and after therapy by examining biopsy specimens by immunohistochemistry for EGFR, ERK, and their phosphorylated forms.

PATIENTS AND METHODS

Eligibility

This study enrolled patients with recurrent or metastatic SCCHN who were considered ineligible for curative surgery or radiotherapy. Patients were

Journal of Clinical Oncology, Vol 21, No 10 (May 15), 2003: pp 1980-1987
DOI: 10.1200/JCO.2003.10.051

enrolled at selected centers participating in the University of Chicago Phase II Consortium. Patients were required to have measurable disease as defined by Response Evaluation Criteria in Solid Tumors; were not allowed any prior EGFR-based therapy; were allowed no more than one prior systemic therapy for incurable, recurrent, or metastatic disease; and were allowed no chemotherapy or radiotherapy within 4 weeks of study entry.

Patients had to be at least 18 years of age, nonpregnant, have a life expectancy of 3 months or more, and an Eastern Cooperative Oncology Group performance status of 2 or less. Normal organ and marrow function were necessary and were defined as a leukocyte count $\geq$ 3,000/μL, an absolute neutrophil count $\geq$ 1,500/μL, a platelet count $\geq$ 100,000/μL, a total bilirubin within normal institutional limits, plasma AST and ALT levels $\leq$ 2.5 times the institutional upper limit of normal, and a creatinine level $\leq$ 1.5 mg/dL.

All patients were required to understand and sign the applicable institutional review board's approved informed consent document.

Treatment Plan and Dose Modifications

ZD1839 was administered to all patients at a fixed continuous dose of 500 mg/d. Patients unable to swallow tablets were allowed to dissolve ZD1839 in water. All patients were given baseline ophthalmologic assessments, which included visual acuity and slit-lamp examinations.

Therapy was continued until disease progression, intercurrent illness preventing further administration, unacceptable toxicity, or patient decision. Toxicity was graded using the National Cancer Institute common toxicity criteria version 2.0.

Patients who experienced grade 2 skin rash, nausea, or diarrhea that was unacceptable had therapy temporarily held until resolution to grade 1 or less. If, on restarting therapy, the toxicity continued, the dose was lowered to 250 mg. Other grade 2 nonhematologic toxicities required dose reduction to 250 mg. Any grade 3 or 4 toxicity required temporary discontinuation of therapy until resolution to grade 1 or less and reinstitution at 250 mg. Patients whose toxicity did not resolve after 2 weeks of discontinuation or who required a second dose reduction were removed from study. Once a patient's dose was reduced, it was not subsequently increased.

Response Assessment

Patients were re-evaluated clinically at least every 4 weeks and radiographically every 8 weeks. The same evaluation modality was used throughout the study. Response guidelines as defined by Response Evaluation Criteria in Solid Tumors were used,[14] defining all responses after at least 8 weeks of therapy as either a complete response (CR), a partial response (PR), progressive disease (PD), or stable disease (SD). We defined disease control as the sum of patients achieving a CR, PR, or SD. Confirmation of all responses was required after 4 weeks. The National Cancer Institute's Clinical Trials Monitoring Branch independently reviewed all patients who responded, had tumor shrinkage, or had prolonged stable disease.

Biopsy and Tissue Preparation

Patients who had accessible tissue were randomly assigned to undergo biopsy either before therapy (pre) or at 7 weeks of therapy (post). Biopsies were performed with 1% xylocaine on an outpatient basis using a 14-guage biopsy needle. Tissue was instantly placed in Tissue Freezing Medium (Triangle Biomedical Sciences, Durham, NC) and 2-methylbutane in liquid nitrogen and stored at -80°C. The study biopsies were stained for EGFR, ERK, and phosphorylated ERK (p-ERK)–tyrosine residue 204 on ERK-1.

Immunohistochemistry

The frozen tissues were sectioned into 6-μm slices and fixed in 4% paraformaldehyde for 10 minutes. After the slides were rinsed, they were incubated in 3% hydrogen peroxide for 5 minutes and then 10% normal goat serum in 0.025% Triton X-100 phosphate-buffered saline for 20 minutes. The slides were incubated with either ERK-1 (1 μg/mL; Santa Cruz Biotechnology, Santa Cruz, CA), p-ERK (8 μg/mL; Santa Cruz Biotechnology), or EGFR antibody (1:25; Cell Signaling Technology, Beverly, MA) for 1 hour at room temperature in a humidity chamber. After slides were washed in phosphate-buffered saline, they were incubated with EnVision Systems (DAKO A/S, Glostrup, Denmark) antimouse or antirabbit kit for 30 minutes at room temperature. The antigen-antibody binding was detected by 3,3′-diaminobenzidine chromogen system (DAKO A/S). The slides were briefly immersed in hematoxylin for counterstaining and evaluated by light microscopy. ERK and p-ERK negative controls used both peptide absorption blocking and isotype-specific immunoglobulin. Isotype-specific immunoglobulin was used as a negative control for EGFR.

Samples that were adequate were evaluated further using a 4-point scoring system on the basis of the number of cells that stained positively (0 = no staining; 1+ = < 10%; 2+ = 10% to 50%; 3+ = > 50%). Histologic examination was performed on all samples by a single pathologist (W.R.) who was blinded to timing of biopsy and response data.

Statistical Analysis

The trial used a two-stage design requiring the enrollment of 22 patients onto the first stage and an additional 24 patients onto the second stage. If at the end of the first stage fewer than two responses were observed and more than 14 patients experienced disease progression within 2 months, the trial would be stopped. Otherwise, if more than five responses were observed or fewer than 29 patients experienced disease progression within 2 months among the total 46 patients, this would be sufficient to reject the null hypothesis and conclude that ZD1839 warrants further study. This design provided an alpha level of 10% and a power between 0.74 and 0.90, depending on different alternative scenarios.

The primary end points were response rate and time to progression (TTP). Secondary end points included survival, toxicity, and correlations of staining with response. All patients who met eligibility criteria and were assessable for response were included in the efficacy analysis. All patients who were registered and received drug were included in the toxicity analysis. Data were updated to June 24, 2002.

TTP and survival were measured from date of registration until disease progression or death, respectively, and were summarized by Kaplan-Meier curves. Factors related to response or lack of early progression were analyzed using the Fisher's exact test, and factors related to survival were analyzed using the log-rank test and Cox proportional hazards model. Staining intensity comparison was performed using a Wilcoxon rank sum test. The correlation between the staining level and tumor response was evaluated using a Wilcoxon rank sum test. All statistical analyses were conducted at the .05 level of significance.

RESULTS

Patients and Eligibility

Fifty-two patients were enrolled from March to October 2001. Their characteristics are listed in Table 1. Five patients were registered but were not assessable for response for the following reasons: one patient had a serum creatinine level greater than the eligibility limit (this patient never received the drug), one patient died of an unknown cause during cycle 1, two patients on further review did not have head and neck cancer (one patient had non–small-cell lung cancer and one patient had benign disease), and one patient was removed from study because of possible toxicity (transverse myelopathy) during cycle 1. The latter three patients are included in the toxicity analysis.

Prior therapy administered to the 47 assessable patients is listed in Table 1. Prior chemotherapy was administered as either part of an initial curative intent chemoradiotherapy regimen (n = 30) or as palliative treatment of incurable disease (n = 23). Of the 40 patients (85%) who received chemotherapy at any time during their treatment, 28 (70%) had a prior platinum-containing regimen. Half the patients (49%) had experienced treatment

Table 1. Patient Demographics

Characteristic	Patients No.	Patients %
Total	52	100
Male	40	77
Female	12	23
Age, years		
Median	59	
Range	34-84	
Disease status at enrollment		
Locally recurrent	23	44
Metastatic*	29	56
ECOG performance status†		
0	10	21
1	29	62
2	8	17
Prior therapy (n = 47)		
Surgery	42	89
Radiotherapy	45	96
With chemotherapy	30	67‡
Alone	15	33‡
Chemotherapy	40	85
As part of the radiotherapy	17	43‡
As part of radiotherapy then for recurrent/metastatic disease§	13	33‡
Only for recurrent or metastatic disease§	10	25‡

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*These patients may also have had local recurrence simultaneously with metastatic disease.

†This is reported for the 47 assessable patients.

‡These data reflect percentages of the subgroup, ie, radiotherapy or chemotherapy.

§Twenty-three patients (49% of total assessable) received a prior regimen for recurrent/metastatic disease.

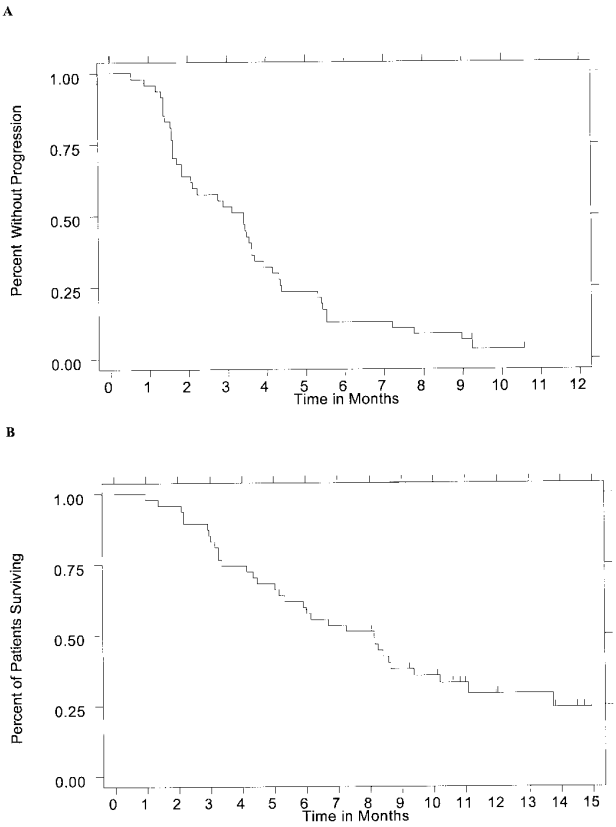

Fig 1. Kaplan-Meier curve of (A) time to progression and (B) overall survival.

failure with a prior systemic regimen for incurable recurrent or metastatic disease and therefore received ZD1839 as second-line palliative therapy. The median time from completing prior therapy to registration was 4 months (range, 1 to 78.8 months).

The protocol allowed administration of ZD1839 via feeding tube. In total, 14 patients received ZD1839 via this route. This group, albeit small, did not exhibit any clinical or statistical differences with respect to response, toxicity, or survival compared with patients who took ZD1839 orally.

Follow-up for patients continued after disease progression until death. In total, 14 patients received subsequent therapy consisting of chemoradiotherapy in three patients and systemic chemotherapy in 11 patients.

Treatment Responses

Two patients had either CR or PR and nine patients experienced disease progression within 2 months among the 22 patients entered during the first stage; five patients had either CR or PR and 22 patients experienced disease progression within 2 months among the first 46 assessable patients. Thus from this standpoint, the drug can be declared sufficiently active to warrant further study. Of the total 47 assessable patients, we observed one CR and four PRs for an overall response rate of 10.6% (95% confidence interval [CI], 3.5% to 23.1%). A total of 20 patients (42.6%) had SD (95% CI, 28.3% to 57.8%) as their best response, including five patients experiencing minor responses that did not meet criteria for PR. Therefore, as defined above, 53% of the patients experienced some degree of disease control. The remaining 22 patients (46.8%) had progressive disease at initial re-evaluation (95% CI, 32.1% to 61.9%).

Of the responding patients, three had metastatic disease (visceral or soft tissue) and two had local recurrences. At last update, four of the five responders had experienced disease progression, with a median duration of response of 1.6 months (range, 1.2 to 11 months).

TTP and Survival

In total, 45 patients have eventually developed progressive disease, with two patients remaining on study (Fig 1A). The median TTP was 3.4 months (95% CI, 1.8 to 3.6 months). By 3, 6, and 9 months, 53.2%, 12.8%, and 6.4% of patients, respectively, had not experienced disease progression.

With a median follow-up time of 11.4 months, median survival has reached 8.1 months (95% CI, 5.2 to 9.4 months) for the entire cohort, with a 1-year survival probability of 29.2% (Fig 1B). Of the 47 assessable patients, 14 are still alive.

Toxicity

Fifty patients were included in the toxicity analysis. One patient never received ZD1839 and one patient died during cycle

Table 2. Toxicity Observed by Grade

Toxicity	%* of Patients	Grade 1	2	3	4
Skin	48	15	9	0	0
Keratitis	4	0	2	0	0
Anorexia	26	8	2	3	0
Nausea	18	5	2	2	0
Vomiting	12	2	4	0	0
Diarrhea	50	18	4	3	0
ALP	4	1	1	0	0
AST	12	5	1	0	0
ALT	4	2	0	0	0
Hypercalcemia	20	5	2	2	1
Creatinine	2	0	1	0	0
Dyspnea		1	2	0	0

Abbreviation: ALP, alkaline phosphatase.
*Fifty patients were assessable for toxicity.

Table 3. Factors Related to Response

Factor	CR/PR/SD No.	%	PD No.	%	P*
Performance status					
0	8	32	2	9	.001
1	17	68	12	55	
2	0		8	36	
ZD1839 as					
Second-line therapy	12	48	11	50	.99
First-line therapy	13	52	11	50	
Prior chemoradiotherapy					
Yes	16	64	14	64	.99
No	9	36	8	36	
Any chemotherapy					
Yes	22	88	18	82	.69
No	3	12	4	18	
Skin toxicity					
Yes	17	68	5	24	.004
No	8	32	16	76	
Diarrhea					
Yes	17	68	8	38	.074
No	8	32	13	62	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Fisher's exact test.

1 without toxicity data available. Toxicities encountered are listed in Table 2. The most common toxicities observed were dermatologic and gastrointestinal. The integumentary toxicity included an acneiform skin rash, brittle hair, and onycholysis. Of the 24 patients who developed skin toxicity, 20 did so in cycle 1 and an additional two patients did so by cycle 2. The only patient to discontinue therapy because of toxicity did so by choice because of intolerable acneiform rash (grade 2). As listed in Table 2, the most common gastrointestinal toxicity was diarrhea, which required dose reduction in four patients (three patients with grade 3 and one patient with grade 2 diarrhea). Subsequent to dose modification, all patients were able to continue therapy at the lower dose.

Some adverse events encountered during the trial were possibly related to the agent or the disease. One patient experienced cervical myelopathy with urinary and stool incontinence 7 days after starting ZD1839. These symptoms abated and completely resolved within 4 weeks of discontinuing therapy. Magnetic resonance imaging of the spinal cord at the time was nondiagnostic.

Three patients developed cellulitis at sites of active skin involvement during therapy. The findings consisted of marked inflammation with warmth and erythema. Although an infectious diagnosis was made, cultures were sterile in all cases. In addition, three patients experienced hemorrhages at disease sites while receiving therapy. One of these events was fatal, whereas another required transfusion of two units of packed RBCs. Both of these patients had tumor shrinkage radiographically.

As shown in Table 2, 20% of patients on study experienced some degree of hypercalcemia. None of these patients had evidence of bone metastasis. In all but one of these patients (a patient with a transient grade 1 value), the finding of hypercalcemia preceded radiographic evidence of nonskeletal disease progression at their next evaluation.

Factors Related to Response, Progression, and Survival

Additional analysis of factors related to disease control revealed that only performance status and development of skin toxicity were predictive (Table 3) Prior therapy of any kind, duration from prior therapy, or administration of ZD1839 as first- or second-line therapy did not predict for response or disease control.

Factors related to progression are shown in Table 4. Similar to the response analysis, baseline performance status was strongly associated with TTP ($P < .0001$). Because development of skin toxicity was closely linked with disease control, this toxicity also predicted longer progression-free survival (4.3 *v* 2.1 months; $P = .0002$). In addition, patients who enrolled with metastatic disease experienced disease progression more rapidly than did those with locally recurrent disease (2.8 *v* 4.1 months; $P = .03$).

A number of factors were associated with favorable survival, including baseline performance status ($P < .0001$), achieving a response ($P = .0002$) or disease control ($P = .0001$), and development of skin toxicity (Table 5 and Fig 2). Interestingly, patients who developed skin toxicity had a greater than two-fold median survival compared with patients who did not (11.1 *v* 5.3 months; $P = .001$). The only other toxicity encountered with frequency (diarrhea) did not predict survival ($P = .12$). There was a nonsignificant trend toward improved survival in patients receiving ZD1839 as first-line therapy ($P = .25$).

A multiple Cox proportional hazards model was used to identify independent prognostic factors of survival. In the unadjusted analysis, development of skin rash carried a hazard ratio of death of 0.30 (95% CI, 0.14 to 0.65). When performance status was adjusted for, patients with skin toxicity had a longer survival ($P = .046$), with a hazard ratio of 0.43 (95% CI, 0.19 to 0.98). However, after adjustment for disease control, skin rash was not independently predictive of survival, with a hazard ratio of 0.49 (95% CI, 0.21 to 1.18), likely because of a strong correlation of skin rash with disease control. Conversely, disease control predicted prolonged survival when performance status or

Table 4. Factors Related to Time to Progression

Factor	No. of Patients	Median TTP (months)	95% CI	3 Months* (%)	6 Months* (%)	P†
Performance status						
0	10	5.4	1.6 to 9.0	80	40	< .0001
1	29	3.4	1.8 to 3.6	59	7	
2	8	1.6	0.6 to 2.1	0	0	
Disease status						
Metastasis	28	2.8	1.6 to 3.5	46	7	.03
Recurrent	19	4.1	2.1 to 5.4	63	21	
ZD1839 as						
First-line therapy	23	3.4	1.7 to 3.5	57	4	.35
Second-line therapy	24	3.6	1.6 to 5.4	50	21	
Any prior chemotherapy						
Yes	40	3.4	2.1 to 3.9	58	13	.15
No	7	1.4	0.6 to 3.7	29	14	
Skin toxicity						
Yes	22	4.3	3.1 to 5.5	77	23	.0002
No	24	2.1	1.6 to 3.4	33	4	
Diarrhea						
Yes	25	3.6	2.8 to 5.3	68	16	.12
No	21	1.8	1.6 to 3.4	38	10	

Abbreviations: TTP, time to progression; CI, confidence interval.
*Three- and 6-month columns represent percentage of patients who did not experience disease progression.
†*P* value for log-rank test.

skin toxicity were adjusted for (hazard ratio = 0.40 [95% CI, 0.17 to 0.91] or 0.38 [95% CI, 0.16 to 0.88], respectively).

Pharmacodynamic Studies

A total of 14 samples were collected, 10 of which were adequate for interpretation: six before (pre) and four at 7 to 8 weeks of therapy (post). The results of immunohistochemical staining are tabulated in Table 6. There was no difference statistically in EGFR ($P = .13$) staining intensity between the pre- and posttherapy samples. However, ERK staining intensity was statistically higher in the posttherapy samples ($P = .02$). Despite the higher intensity of ERK staining in the posttherapy samples, a consequent increase in p-ERK staining intensity was not observed ($P = .90$ for p-ERK pre *v* post). A correlation between response and staining was not observed for any of the proteins, although the value for patients who stained lower for p-ERK did approach significance ($P = .11$).

DISCUSSION

This is the first clinical trial to use ZD1839, a small-molecule tyrosine kinase inhibitor (TKI) of EGFR, in SCCHN. With 47 assessable patients, the study was able to demonstrate activity and tolerability of this agent in patients with incurable disease. Although the overall response rate was modest (10.6%), fewer than half of the cohort experienced disease progression at first evaluation, with favorable TTP (3.4 months) and median survival (8.1 months). These results would compare reasonably well with reported data of single-agent or combination chemotherapy regimens in phase III trials, with the added benefit of less toxicity.[1-6,15-17]

Other EGFR inhibitor trials in SCCHN have shown remarkably similar results. Cetuximab, a monoclonal antibody directed at the EGFR, yielded response rates of 11% when combined with platinum therapy in two separate phase II trials in platinum-refractory patients[18,19] and 23% when combined with cisplatin as first-line therapy.[20] Another small-molecule TKI, OSI-774, given to patients similar to those in our study produced a response rate of 6%.[21] The acneiform skin rash reported here has been consistently observed in all trials of EGFR inhibitors.[13,22-28]

The acneiform skin rash is of special interest because it likely represents a toxicity that is inherently related to these agents' mechanism of action. Other reports have noted a correlation between the presence of the rash and response—an association that has not retained statistical significance when rash is related to TTP or survival.[18,19,29] Nevertheless, in this study, development of rash was associated with statistically and clinically meaningful improvements in TTP and overall survival, likely related to the strong correlation observed between rash and disease control. Notably, however, two large monotherapy trials in non–small-cell lung cancer failed to show a correlation between response and skin rash.[30,31]

These differences between the current study and prior reports could stem from several factors, including the disease studied or the scoring of toxicities. The great majority of patients who developed the rash did so before their first disease re-evaluation at 8 weeks; it is, therefore, unlikely that the association is related to patients being more likely to develop rash the longer they remain on therapy. However, SCCHN is a disease that almost universally expresses EGFR. In addition, the epithelium of the upper aerodigestive tract is closely related to skin both structurally and functionally more so than other mucosal surfaces of gastrointestinal, respiratory, or glandular tissues. Moreover, the investigators in this study counted all integumentary toxicity, including hair and nail, and asked patients to undress for a full

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