

## Phase I Study of Gefitinib Plus Celecoxib in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

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### ABSTRACT

#### Purpose

Effective and tolerable palliative treatments are needed for patients with incurable squamous cell carcinoma of the head and neck (SCCHN). Single-agent targeted therapies have limited activity in this setting. The feasibility of adding celecoxib to gefitinib for the treatment of incurable SCCHN is unknown.

#### Patients and Methods

Nineteen patients with unresectable recurrent locoregional and/or distant metastatic SCCHN with progressive disease after at least one prior chemotherapy or chemoradiotherapy regimen were enrolled onto this single-institution phase I study. Three dose levels were explored: (1) celecoxib 200 mg twice daily plus gefitinib 250 mg daily; (2) celecoxib 400 mg twice daily plus gefitinib 250 mg daily; and (3) celecoxib 400 mg twice daily plus gefitinib 500 mg daily.

#### Results

No dose-limiting toxicities were encountered at any dose level. The most common toxicities were acneiform rash, diarrhea, hand reaction, dyspepsia, and anemia. Four of 18 patients assessable for response (22%; 95% CI, 2% to 42%) achieved a confirmed partial response.

#### Conclusion

The combination of gefitinib 500 mg daily plus celecoxib 400 mg twice daily is well-tolerated. The encouraging responses seen in this early study suggest further evaluation of epidermal growth factor receptor and cyclooxygenase-2 inhibitors in SCCHN is warranted.

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### INTRODUCTION

An estimated 39,250 new cases of squamous cell carcinoma of the head and neck (SCCHN) will be diagnosed in the United States in 2005.<sup>1</sup> Throughout the last 25 years, major advances in surgical, radiation, and chemotherapeutic approaches to SCCHN have been made, and these advances are finally becoming apparent in survival statistics. For example, for the periods from 1974 to 1976, and from 1995 to 2000, data from the National Health Statistics and the Surveillance, Epidemiology, and End

Results program showed that 5-year survival of patients with oral cavity and pharyngeal carcinomas increased from 54% to 59% ( $P < .05$ ).<sup>1</sup> Still, as these statistics imply, even with modern multimodality treatment approaches, approximately 40% of patients diagnosed with SCCHN will develop incurable disease at some point in the course of their illness.

The treatment of choice for locally recurrent SCCHN is, whenever feasible, salvage surgery or radiation-based therapy. In patients for whom a salvage approach is not possible or who have distant metastatic

disease, palliative systemic therapy is the only option. Both combination and single agent chemotherapy regimens have demonstrated moderate response rates in this setting of approximately 30% to 40%, yet the duration of response is often brief, and median survival is short, typically 6 to 9 months.<sup>2</sup>

Recently, targeted therapies have been explored in attempts to improve on the poor outcomes in incurable SCCHN. To date, drugs targeting the epidermal growth factor receptor (EGFR) have experienced the most clinical development. EGFR is overexpressed in the majority of SCCHNs, and this overexpression correlates with poor prognosis.<sup>3</sup> This, coupled with the understanding of the downstream consequences of EGFR signaling, including cell proliferation, suppression of apoptosis, and tumor angiogenesis, has made EGFR an appealing target in SCCHN.<sup>4,5</sup> EGFR inhibitors that have undergone the most clinical development in SCCHN are the monoclonal antibody, cetuximab, and the small molecule tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib. As single agents, EGFR inhibitors are well tolerated, but thus far, they have shown only modest activity against SCCHN, with estimated response rates ranging from 3.5% with gefitinib at 250 mg daily, and 10.6% at 500 mg daily, to 11% to 14% with cetuximab administered weekly.<sup>6-9</sup>

One strategy to enhance the efficacy of anti-EGFR therapy while maintaining tolerability is to add in another targeted therapy with nonoverlapping toxicity. As with EGFR, cyclooxygenase-2 (COX-2) is overexpressed in SCCHN, and its expression correlates with poor prognosis.<sup>10</sup> COX-2 is an inducible enzyme that results in an array of downstream events, including suppression of apoptosis and activation of proliferation and angiogenesis. Of note, there is interaction between EGFR and COX-2 signaling pathways at several levels. For example, EGFR and COX-2 both signal through the ras/MAPK and PI3K/Akt pathways.<sup>11</sup> Crosstalk between EGFR and COX-2 has also been demonstrated at the level of activation. That is, EGFR-mediated MAPK activity can induce COX-2 expression.<sup>12</sup> In turn, COX-2, via its primary mediator, PGE<sub>2</sub>, can activate the cyclic AMP/protein kinase A pathway to promote the expression amphiregulin, one of several EGFR ligands.<sup>13</sup> The potential for enhanced activity of combining EGFR and COX-2 blockade, as suggested by these interactions, has been confirmed in preclinical combination studies of EGFR TKIs plus COX-2 inhibitors. One such study showed that combined therapy inhibited growth in at least an additive fashion in five SCCHN cell lines.<sup>14</sup> In vivo, combination therapy has been tested in the intestinal neoplasia *APC*<sup>Min/+</sup> mouse model. EGFR was targeted with the TKI EKI-569, and COX-2 was inhibited by the nonsteroidal anti-inflammatory drug, sulindac. Alone, these agents reduced polyp formation by 87% and 70%, respectively, whereas combined treatment yielded a greater than 95% reduction in polyps, suggesting that this combination has more potent antiproliferative activity than either agent alone.<sup>15</sup>

We therefore undertook this phase I study to establish the appropriate dosing and safety profile of gefitinib plus the COX-2 inhibitor, celecoxib, in subjects with incurable SCCHN, as a first step to exploring the combined targeting of EGFR and COX-2 in this disease.

## PATIENTS AND METHODS

### Patients

Between May 2003 and April 2004, 19 patients with incurable SCCHN were enrolled onto this phase I study at Dana-Farber Cancer Institute and Massachusetts General Hospital. The protocol was approved by the Dana-Farber/Harvard Cancer Center Office for the Protection of Research Subjects. Eligibility criteria included unresectable recurrent locoregional and/or distant metastatic SCCHN, with progressive disease after at least one prior chemotherapy or chemoradiotherapy regimen. Subjects also were required to have assessable disease; life expectancy  $\geq$  4 months; Eastern Cooperative Group performance status of  $\leq$  2; adequate hematologic, renal, and liver function; use of sufficient birth control in women of childbearing potential; and signed informed consent. Exclusion criteria included hypersensitivity to celecoxib, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs); significant comorbidities (including coronary artery disease, symptomatic congestive heart failure, active alcohol abuse, bleeding diathesis, history of interstitial lung disease or gastrointestinal ulcer within 12 months); other malignancy except basal cell skin carcinoma or cervical carcinoma-in-situ; concomitant use of phenytoin, carbamazepine, barbiturates, rifampin, phenobarbital, St John's Wort, aspirin at a dose of 325 mg daily or higher, NSAIDs, rofecoxib, or other COX-2 inhibitors; or systemically absorbed steroids, surgery, or radiotherapy within 30 days; pregnancy; or breast-feeding.

### Dose Levels and Treatment

Table 1 illustrates study dose levels. Celecoxib was administered at 200 mg by mouth twice daily, with gefitinib 250 mg by mouth once daily in dose level 1. Subjects unable to take medications by mouth were administered both drugs by gastric tube. Dose level 2 consisted of celecoxib 400 mg twice daily plus gefitinib 250 mg/d. Dose level 3 consisted of celecoxib 400 mg twice daily plus gefitinib 500 mg/d. One cycle equaled 28 days of continuous treatment.

Nonhematologic dose-limiting toxicity (DLT) was defined as National Cancer Institute Common Toxicity Criteria (CTC), version 2.0 grade 4 skin rash occurring in cycle 1 of treatment, grade  $\geq$  3 skin rash on reduced doses of gefitinib, grade  $\geq$  3 diarrhea on reduced doses of gefitinib, grade 4 diarrhea with hemodynamic collapse, grade  $\geq$  3 gastritis or gastric ulcer on reduced doses of

**Table 1.** Dose Levels

Dose Level	Gefitinib (mg QD)	Celecoxib (mg bid)
1	250	200
2	250	400
3	500	400

Abbreviations: QD, daily; bid, twice daily.

gefitinib and/or celecoxib, grade  $\geq 3$  gastrointestinal hemorrhage, grade  $\geq 3$  allergic reaction, grade  $\geq 3$  pneumonitis, or other grade  $\geq 3$  nonhematologic toxicity on reduced doses of gefitinib and/or celecoxib. Hematologic DLT was defined as “clinically relevant CTC grade  $\geq 3$  hematologic toxicity” (ie, absolute neutrophil count  $< 1.0 \times 10^9/L$ ) for more than 7 days, fever ( $> 38.5^\circ C$ ) with neutropenia, platelet count less than  $50 \times 10^9/L$ , and/or grade 4 anemia. Three patients were enrolled at each dose level. Enrollment proceeded to the next dose level after all three patients were treated for  $\geq 4$  weeks and safety data were reviewed. If no DLTs occurred, the next dose level was opened. If one DLT occurred, three additional patients were enrolled at the current dose level. If no additional DLT occurred, enrollment continued at the next level. If an additional DLT occurred (ie, two or more DLTs per six patients), then the previous dose level would be declared the maximum tolerated dose (MTD). If two DLTs occurred, no further dose escalation would be done, and the previous dose level would be declared the MTD. If the MTD would not be reached because one or zero DLTs were encountered at dose level 3, this dose would be considered the maximum dose, and 10 additional patients would be enrolled at this dose or the MTD to gain additional experience with this regimen.

Tumor assessment for response took place at the end of every two cycles (ie, 8 weeks) of therapy. In patients completing six cycles of therapy, the evaluation for response was performed after every third cycle. Response was assessed radiographically according to Response Evaluation Criteria in Solid Tumors (RECIST) and by physical examination including fiberoptic endoscopy of the head and neck. Patients with stable disease or better, continued treatment with gefitinib and celecoxib until progressive disease or unacceptable toxicity. Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method from the start of therapy until, respectively, disease progression, and date of death or last follow-up.

### Assessment of Potential Biomarker Predictors of Response

All available formalin-fixed paraffin-embedded patient tissue samples were evaluated for tumor content by available hematoxylin and eosin-stained slides. Tumor was dissected from normal-appearing tissue by manual microdissection, and DNA extracted. Exons 18 to 24 of *EGFR* were evaluated for mutations by amplification using nested primers. Polymerase chain reaction (PCR) products were then sequenced in both sense and antisense directions as previously described.<sup>16,17</sup> Exons 2 and 3 of *KRAS* were amplified in a set of individual nested PCR reactions. The primers used in the external PCR amplification were as follows: exon 2 forward: 5' CTTAAGCGTTCGATGGAGGAG; exon 2 reverse: 5' CCCTGACATACTCCCAAGGA; exon 3 forward: 5' TGGGTATGTGGTAGCATCTCA; exon 3 reverse: 5' AATCCCAGCACCACTACTAC. The primers used in the internal PCR amplification were as follows: exon 2 forward: 5' GTGTGACATGTTCTAATATAGTCA, exon 2 reverse: 5' GAATGGTCCTGCACCAGTAA; exon 3 forward: 5' TCAAGTCCTTTGCCCATTTT, exon 3 reverse: 5' TGCATGGCATTAGCAAAGAC.<sup>18</sup> Universal linker sequences were added to the 5' ends of the internal primers (forward 5'TGTAACGACGGCCAGT; reverse 5'AACAGCTATGAC-CATG). PCR products were sequenced bi-directionally by dye-terminator sequencing using a universal primer. Sequence analysis was performed by Mutation Surveyor (SoftGenetics, State College, PA), and manually by two reviewers. The *KRAS* exon 2 and 3 analyses were conducted by the Laboratory for Molecular Med-

icine of the Harvard Medical School/Partners Healthcare Center for Genetics and Genomics (CLIA# 22D1005307). *EGFR* and *KRAS* amplification was investigated by quantitative real-time PCR performed on a PRISM 7700 sequences detector (Applied Biosystems, Foster City, CA), using a QuantiTect SYBR Green kit (Qiagen Inc, Valencia, CA). The standard curve method was used to calculate target gene copy number. PCR sequences for each target used are as previously described.<sup>19</sup> PCR reactions were performed at least in duplicate, and means are reported. Amplification ratios  $\geq 2.0$  were considered indicative of gene amplification.

## RESULTS

### Patient Characteristics

Nineteen patients were enrolled on study (Table 2). The median age was 55 years (range, 26 to 68 years). Nine patients (47%) had recurrent unresectable locoregional SCCHN, five (26%) had distant metastatic SCCHN, and five (26%) had both locoregional and distant metastatic disease. All patients had received at least one prior chemotherapy or chemoradiotherapy regimen. Eight patients started on study at the time of relapsed disease following definitive chemoradiotherapy, two patients were enrolled after progressive disease following reirradiation with con-

Table 2. Patient Characteristics

Characteristic	Patients	
	No.	%
Age, years		
Median	55	
Range	29-68	
Sex		
Male	16	84
Female	3	16
Ethnicity		
White	18	95
Hispanic	1	5
ECOG PS		
0	13	68
1	5	26
2	1	5
Site of disease		
Locoregional recurrence	9	47
Distant metastasis	5	26
Both	5	26
Prior therapy		
Primary site surgery	3	16
MRND	10	53
Radiotherapy	6	32
Chemoradiotherapy	14	74
Reirradiation/concurrent chemotherapy	2	11
Induction chemotherapy	9	47
Palliative chemotherapy	9	47

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; MRND, modified radical neck dissection.

current chemotherapy, and nine patients were treated after progression on palliative chemotherapy following prior definitive therapy. Overall, a total of 91 cycles of gefitinib and celecoxib were administered, with a median of three cycles per patient. Three patients were treated at dose levels one and two, and 13 patients were treated at dose level three.

### Toxicities

No DLTs were encountered at any dose level. Adverse events deemed at least possibly related to therapy by study investigators are described. The most common toxicities encountered were acneiform rash, diarrhea, hand reaction, dyspepsia and anemia (Table 3). Ten patients (53%) treated across all three dose levels experienced grade 1 or 2 acneiform rash. Two patients (11%), both treated in dose level 3, developed grade 3 acneiform rash. Eleven patients (58%) treated across all three dose levels experienced diarrhea. One patient in dose level 1 was treated for grade 3 diarrhea during cycle 3. The diarrhea resolved after gefitinib was held for 6 days and the patient received intravenous fluids, loperamide, atropine sulfate/diphenoxylate hydrochloride, and octreotide. All other cases of diarrhea were grade 1 or 2. Six patients (32%) developed grade 1 or 2 hand reaction (erythema with or without peeling or pain). Four patients (21%), one in dose level 1 and three in dose level 3, experienced grade 1 or 2 dyspepsia. Six patients (32%) experienced grade 1 anemia: one each in dose levels 1 and 2 and four in dose level 3. No other hematologic toxicities were

seen. Celecoxib was discontinued in one patient due to allergic drug eruption of grade 2 severity, and in one patient due to grade 3 renal insufficiency. Both patients continued gefitinib alone until disease progression. Other toxicities encountered were: grade 1 nausea (n = 3), grade 1 vomiting (n = 2), paronychia (n = 2), and grade 2 dehydration (n = 1). One patient experienced grade 2 seizure (n = 1), which was thought to be unrelated to treatment. One patient experienced a fatal internal carotid artery hemorrhage after 66 weeks of treatment. This event was considered unlikely to be related to treatment and was attributed to progressive disease. No cases of interstitial lung disease or cardiovascular events were encountered, and no dose reductions were required throughout the study period.

### Response and Survival

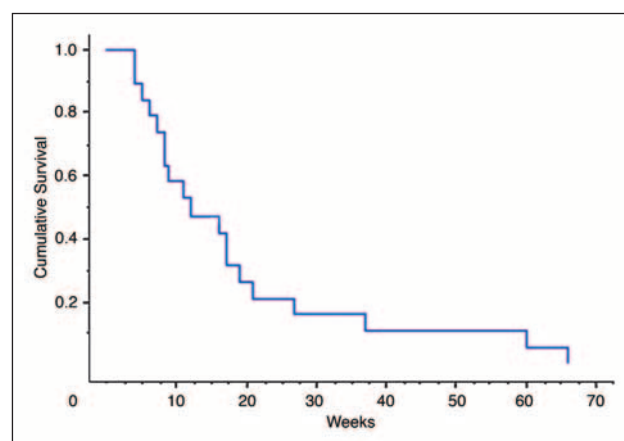
One patient in dose level 3 was lost to follow-up at 4 weeks, and was thus not assessable for response. Four of eighteen patients (22%; 95% CI, 2% to 42%) achieved a confirmed partial response (PR). No complete responses were seen. Responses were seen in all dose levels. One occurred in dose level 1, two in dose level 2, and one in dose level 3. Six patients (33%; 95% CI, 11% to 55%) achieved stable disease (SD). The median duration of response was 19 weeks (range, 16 to 66 weeks), or 4.8 months. The median PFS and OS times were 12 weeks (range, 4 to 66 weeks) and 24 weeks (range, 11 to 70 weeks), respectively (Figs 1 and 2). Of particular interest were two cases of prolonged therapy with gefitinib and celecoxib. One patient who was heavily pretreated for multiply recurrent locoregional disease experienced an impressive durable response lasting 66 weeks. Another patient who had numerous lung metastases following induction chemotherapy and chemoradiotherapy had SD lasting for 60 weeks.

### Biomarkers Assessment

Formalin-fixed paraffin embedded tumor tissue was available for 12 of the 19 patients. PCR for *EGFR* and *KRAS*

Toxicity	All Patients		Dose Level		
	No.	%	1 (n = 3)	2 (n = 3)	3 (n = 13)
<b>Rash</b>					
Grade 1-2	10	53	1	2	7
Grade 3	2	11	—	—	2
Total	12	63	1	2	9
<b>Diarrhea</b>					
Grade 1-2	10	53	1	2	8
Grade 3	1	5	—	—	—
Total	11	58	1	2	8
<b>Hand reaction</b>					
Grade 1-2	6	32	2	2	2
Grade 3	—	—	—	—	—
Total	6	32	2	2	2
<b>Dyspepsia</b>					
Grade 1-2	4	21	1	—	3
Grade 3	—	—	—	—	—
Total	4	21	1	—	3
<b>Anemia</b>					
Grade 1-2	6	32	1	1	4
Grade 3	—	—	—	—	—
Total	6	32	1	1	4

NOTE. Toxicity grades are according to National Cancer Institute Common Toxicity Criteria, version 2.0.



**Fig 1.** Progression-free survival.

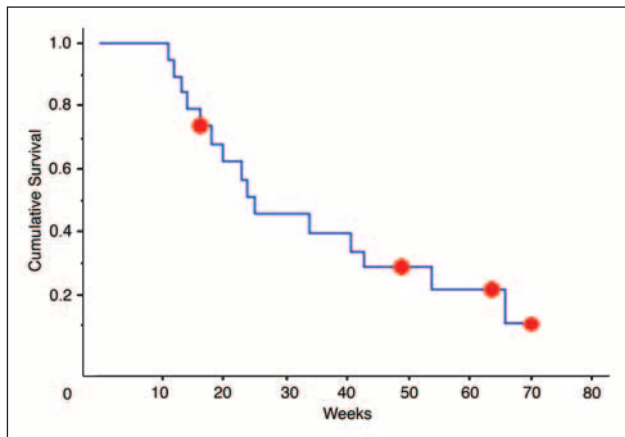


Fig 2. Overall survival.

failed from two of these 12 specimens. Of the 10 remaining specimens, one came from a patient with a PR to treatment, four were from patients with SD, and five were from patients with PD. No mutations were found in *EGFR* exons 18 to 24 or *KRAS* exons 2 and 3. *EGFR* and *KRAS* amplification was determined by quantitative PCR in these 10 specimens. *EGFR* was not amplified in any tumor studied, while four of 10 specimens (40%) were found to have amplified *KRAS* with copy numbers ranging from five to 20.

## DISCUSSION

This study has shown that gefitinib plus celecoxib is a low-toxicity, well-tolerated regimen in patients with incurable, unresectable previously treated SCCHN. No DLTs were encountered at any dose level. In SCCHN, there is a strong rationale for investigating the 500 mg dose, given the higher response rate seen with 500 mg in phase II study compared with that seen with 250 mg.<sup>6,7</sup> Further dose escalation of gefitinib beyond 500 mg daily was, however, not considered in light of data from a large study in advanced non-small-cell lung cancer randomizing patients between 250 mg and 500 mg that showed no difference between the two doses with respect to response, survival or overall symptoms, whereas acneiform rash and diarrhea were both increased with the higher dose, suggesting that gefitinib dose escalation offers limited benefit.<sup>20</sup> Therefore, we conclude that the recommended dose for future phase II study is gefitinib 500 mg per day plus celecoxib 400 mg twice daily.

Prior phase II studies of gefitinib alone at doses of 500 mg and 250 mg daily in a similar pretreated SCCHN population showed that the principal gefitinib-related toxicities of rash and diarrhea are comparable to those seen in this study.<sup>6</sup> For example, with gefitinib alone, 48% and 64% of

patients experienced grade 1 to 2 rash at 500 mg and 250 mg daily, respectively. No  $\geq$  grade 3 rash was seen. In our study, 64% of patients had skin rash. Two cases were grade 3, all others were grade 1 to 2. In the prior studies, diarrhea occurred in 50% (6% grade 3; all others grade 1-2) and 30% (3% grade 3; all others grade 1 to 2) of patients, respectively. With this combination of gefitinib plus celecoxib, 58% of patients experienced diarrhea (5% grade 3; all others grade 1 to 2). Additional toxicities encountered with this combination were occasional dyspepsia, infrequent allergic drug eruption and renal insufficiency. Therefore, the addition of celecoxib to gefitinib does not seem to affect the degree of gefitinib-specific toxicity, but does contribute celecoxib-related toxicities to the side effect profile. With the respective overall response rates of 11% and 4% seen in the prior gefitinib single-agent phase II studies, the response rate of 22% in this study is encouraging, particularly in light of the minor increase in toxicity that celecoxib adds to gefitinib. Moreover, impressive durable responses to gefitinib plus celecoxib can be seen. While these results must be interpreted cautiously due to the small sample size of 18 patients and wide 95% confidence intervals, the combination of EGFR and COX-2 inhibitors for the treatment of SCCHN warrants further study.

With the small sample size in this study, evaluation of tumor markers predictive of response was limited. These analyses were even further limited by the success in obtaining tumor tissue and DNA from only one patient with a response to treatment. Nonetheless, we uncovered no evidence to suggest that factors predictive of response to EGFR TKIs in non-small-cell lung cancer (NSCLC), such as mutations in the EGFR tyrosine kinase domain or proto-oncogene *KRAS* involved in signal transduction downstream from EGFR, play a role in SCCHN response to these agents. This is not surprising considering that even though the response rates of NSCLC and SCCHN to EGFR TKIs are similar, the nature of response to therapy is quite different. Most notably, responses to EGFR TKIs in NSCLC are typically dramatic and durable over many months.<sup>21,22</sup> This is in contrast to the less dramatic responses seen in SCCHN, lasting a median of 1.6 months with gefitinib alone in Cohen et al, and 4.8 months with gefitinib and celecoxib in this study.<sup>7</sup> It is most likely that the different responses to EGFR tyrosine kinase inhibition in NSCLC and SCCHN are a consequence of distinct tissue-specific mechanisms in these two diseases. That said, one recent study has identified the same E746-A750 deletion mutation in the EGFR tyrosine kinase domain that is the most common mutation detected in NSCLC in 3 of 41 (7.3%) SCCHN tumors tested.<sup>23</sup> Clearly, there is need for confirmation of EGFR mutations in SCCHN, correlation of mutational status with

response to EGFR TKI therapy and further exploration of the biologic mechanisms of EGFR inhibition in SCCHN.

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### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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