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ORIGINAL REPORT

Phase I/II Trial of Erlotinib and Cisplatin in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck: A Princess Margaret Hospital Phase II Consortium and National Cancer Institute of Canada Clinical Trials Group Study

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ABSTRACT

Purpose
To determine the phase II dose and objective response rate of erlotinib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, in combination with cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC).

Patients and Methods
HNSCC patients with no prior chemotherapy and measurable disease were treated in three escalating-dose cohorts of daily continuous oral (PO) erlotinib and intermittent intravenous (IV) cisplatin given every 21 days. The recommended phase II dose (RPTD) was then evaluated in a two-stage trial with a primary end point of objective response rate.

Results
A total of 51 patients were enrolled. The RPTD was identified as erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV every 21 days. Forty-five patients were treated at the RPTD, of which 44 and 43 were eligible for toxicity and efficacy evaluations, respectively. The intention-to-treat response rate was 21%, with one complete and eight partial responses (95% CI, 10% to 36%), and disease stabilization was achieved in 21 patients (49%; 95% CI, 33% to 65%). Median progression-free survival was 3.3 months (95% CI, 2.7 to 4.8 months) and median overall survival was 7.9 (95% CI, 5.6 to 9.5) months. The combination was well tolerated, with minimal grade 3 or higher toxicity. Subgroup analysis suggested that patients who developed higher grade skin rashes during cycle 1 had better survival outcomes ($P = .034$).

Conclusion
This schedule of erlotinib and cisplatin has a favorable toxicity profile and has antitumor activity in HNSCC comparable to standard combination chemotherapy regimens.

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INTRODUCTION

Large randomized clinical trials that spanned the last decade evaluating combination chemotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC) have demonstrated little progress; median survival remains only 6 to 8 months.[1,2] Although conventional cytotoxic combinations produce objective responses in approximately 25% to 30% of patients, they often cause significant toxicity, and their effects on the quality of life in this population have not been well studied.[2,3] Intensification of chemotherapeutic regimens, such as the use of high-dose paclitaxel in combination with cisplatin and growth factor support in the Eastern Cooperative Oncology Group study E1393, has led to excessive toxicity and failed to improve survival outcome.[4] Such observations have motivated oncologists to continue to seek novel treatments to improve disease control and palliation for these patients.

Multiple lines of evidence support targeting epidermal growth factor receptor (EGFR) as a therapeutic strategy in HNSCC. EGFR is expressed in 80% to 100% of HNSCC, and elevated levels of EGFR and transforming growth factor mRNA have been detected in both tumors and histologically normal mucosa from patients with HNSCC, when compared with control normal mucosa.[5] Clinicopathologic associations between EGFR overexpression and poorer

prognosis have also been reported.[6-8] Current therapeutic strategies targeting EGFR that have found clinical utility include monoclonal antibodies and small molecule tyrosine kinase inhibitors. Erlotinib hydrochloride (erlotinib; N-(3-ethynyphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine; formerly CP-358,774, OSI-774; Tarceva; OSI Pharmaceuticals, Melville, NY) is an orally available, potent, reversible, and selective inhibitor of the EGFR tyrosine kinase. In a large, multicenter phase II study of single-agent erlotinib administered on a continuous schedule of 150 mg once daily, partial responses and disease stabilization were observed, respectively, in 4% and 38% of patients with refractory HNSCC.[9] Cisplatin is the cytotoxic agent with the greatest single-agent activity in HNSCC.[10] In vivo, erlotinib combined with cisplatin produced additive antitumor effects without increased toxicity.[11]

Based on the rationale provided by these observations, a phase I/II trial to evaluate a combination of erlotinib and cisplatin in recurrent or metastatic HNSCC was undertaken. The primary objective of the phase I component was to determine the recommended phase II dose (RPTD) of this combination. The primary objective of the phase II component was to elucidate the efficacy and toxicity of this combination in this population. Secondary objectives included measurements of stable disease rates, duration of responses, progression-free survival (PFS), overall survival (OS), pharmacokinetic profile of erlotinib administered with cisplatin, and pharmacodynamic effects of erlotinib in tumor and skin samples. The latter results are reported separately in a companion article.[12]

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically confirmed diagnosis of recurrent or metastatic HNSCC from any of the primary sites were candidates for this trial. Patients may have had prior induction or concurrent chemotherapy delivered as part of their primary treatment but must have completed primary therapy at least 6 months before study entry. EGFR overexpression was not an inclusion criterion for this study, but all patients must have archival or fresh tumor specimens available and assessable for determination of expression of the EGFR by immunohistochemistry. Other eligibility criteria included age 18 years or older; Eastern Cooperative Oncology Group performance status 0 to 2; ability to swallow tablets, or presence of a silicone-based gastrostomy or jejunostomy feeding tube whereby tablets could be dissolved and administered; measurable disease by Response Evaluation Criteria in Solid Tumors Group criteria[13]; adequate hematopoietic (absolute neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L), hepatic (AST and ALT levels $\leq 2.5\times$ the upper normal limit and bilirubin $\leq 1.25\times$ the upper limit of normal), and renal functions (serum creatinine within normal limits or measured creatinine clearance $\geq$ 60 mL/min); and no prior therapy with EGFR-targeting agents. This trial was approved by the research ethics boards of the participating institutions, and all patients gave written informed consent in accordance with the federal and institutional guidelines before study treatment.

Drug Administration

Erlotinib was administered orally (PO) or via feeding tube on a continuous daily schedule. For cycle 1 only, erlotinib was taken alone for the first 7 days (days −6 to 0) as a run-in period, to enable a steady-state concentration to be reached at the time of cisplatin dosing. After the run-in period, dosing of erlotinib was continued on a daily schedule, with cisplatin given intravenously (IV) on day 1 every 3 weeks. With the exception of cycle 1, which was 4 weeks in length, all subsequent cycles were 3 weeks in length. For cisplatin administration, all patients received adequate hydration and prophylactic antiemetic premedication based on the routine policies of individual institutions. A maximum of six cycles of cisplatin was administered. For patients who achieved and maintained an objective response or disease stabilization after six cycles, erlotinib could continue as a single-agent, with every 3 weeks as one cycle until disease progression.

Phase I and Phase II Components

For the phase I component of this study, three dose levels were evaluated: erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV every 3 weeks; erlotinib 150 mg PO daily and cisplatin 75 mg/m^2 IV every 3 weeks; and erlotinib 150 mg PO daily and cisplatin 100 mg/m^2 IV every 3 weeks. Dose-limiting toxicity (DLT) was defined as the following adverse events considered at least possibly related to the study drug combination occurring during the first cycle: grade 4 neutropenia; febrile neutropenia; grade 3 or 4 documented infection with grade 3 or 4 neutropenia; platelet less than 25×10^9/L; grade 3 or 4 nonhematologic toxicity except alopecia; inadequately managed vomiting or diarrhea; inability to administer day 1 of cycle 2 of either drug with a maximum delay of 2 weeks. The standard 3 + 3 rule was used for dose escalation, and the RPTD was defined as the highest dose level in which no more than one of six patients experienced DLT.

For the phase II component, $P0$ and $P1$ were set at .2 and .4 respectively, with $\alpha = .10$, $\beta = .10$. In the first stage, 17 patients assessable for response would be enrolled, and accrual would proceed to the second stage only if four or more objective responses were observed. This group would include the six patients treated at the RPTD in the phase I portion. In the second stage, 20 additional patients assessable for response would be enrolled, and the regimen would be considered of interest for additional evaluation if at least 11 objective responses were observed out of the total phase II sample size of 37 assessable patients.

Pretreatment and Follow-Up Studies

A complete history and physical examination including a skin assessment, complete blood counts with differential and platelet count, biochemical profile, and urinalysis were measured at screening, at week 1, and then every 3 weeks throughout the study. Adverse events were graded based on the National Cancer Institute Common Toxicity Criteria version 2.0. Objective tumor responses were determined every two cycles according to Response Evaluation Criteria in Solid Tumors Group criteria[13] and underwent central radiology review.

Pharmacokinetic Sampling and Assay

Blood samples were collected before administration of the erlotinib dose on days −6, 1, 15, 22, and 43. The minimum steady-state concentrations ($C_{ss,min}$) of erlotinib and its major metabolite OSI-420 were determined using a validated high-performance liquid chromatography assay with lower limits of quantitation of 12.5 ng/mL for erlotinib and 5 ng/mL for OSI-420.[14]

Statistical Analysis and Sample Size Determination

All patients were considered to be assessable for safety and toxicity if they received any doses of erlotinib. All patients were to be considered assessable for the primary efficacy analysis if they received study drugs, had measurable disease, and had confirmation of disease diagnosis. Patients with disease progression before the end of cycle 2 were evaluated as having experienced early disease progression. PFS and OS were estimated using the Kaplan-Meier method. Two-sided, 95% exact CIs were constructed for outcomes of interest. Rash during cycle 1 as a predictor of OS was performed using a two-sided Cox proportional hazards model with rash defined as an ordinal variable.

RESULTS

Phase I Component

During the phase I component of this trial, three assessable patients were enrolled onto each of three dose levels. DLT was not encountered in dose levels 1 and 2. Two of three patients in dose level 3 encountered DLT, with grade 4 neutropenia in one patient and grade 3 fatigue in another patient. Hence, dose level 3 was deemed to be the maximally administered dose. Although normally the dose level

immediately below would be expanded, a decision was made by study investigators to expand dose level 1 (ie, erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV every 3 weeks). Interestingly, two of three patients treated at dose level 1 achieved partial responses, whereas no objective responses were seen in dose levels 2 and 3. Hence, even though the sample sizes were small, the decision to expand dose level 1 was made due to its favorable therapeutic index. An additional three assessable patients were treated at the expanded dose level 1; one of these three patients developed grade 3 creatinine elevation deemed to be dose-limiting, but no other DLT was seen. Hence, dose level 1 with DLT occurring in one of six assessable patients, was determined to be the RPTD.

Phase II Component

Forty-five patients were treated at the RPTD, including six assessable patients who received the RPTD during the phase I component. One patient enrolled onto the phase II component had rapid disease progression before receiving any study treatment, and was considered ineligible. Hence, 44 patients assessable for toxicity were treated at the RPTD and their baseline characteristics are listed in Table 1. Of the 44 patients, one patient was ineligible for response assessment because there was no measurable disease at baseline on central radiology review. Four of the remaining 43 patients were not assessable for response. Two of these patients were diagnosed to have brain metastases during cycle 1, one patient had grade 3 creatinine elevation during cycle 1 and was removed from study treatment, and one patient withdrew consent during cycle 1.

Table 1. Patient Characteristics for Phase II Cohort Only (N = 44)

Characteristic	No. of Patients	%
Age, years		
Median	56	
Range	24-81	
Sex		
Male	34	77
Female	10	23
Performance status		
0	36	82
1	7	16
2	1	2
Primary disease site		
Oropharynx	13	30
Oral cavity	13	30
Larynx	9	20
Nasopharynx	3	7
Neck mass with unknown primary	3	7
Paranasal sinus	1	2
Salivary glands	1	2
Hypopharynx	1	2
Disease status at study entry		
Locoregional recurrence	16	36
Metastatic	14	32
Both	14	32
Prior therapy		
Surgery	28	64
Radiotherapy	33	75
Chemotherapy	8	18

Safety

Table 2 lists the most frequently observed adverse events considered possibly, probably, or definitely related to study therapy for the 44 patients treated in the phase II cohort at RPTD. Overall, the combination of erlotinib and cisplatin was well tolerated. The most frequent grade 1 to 2 toxicities encountered, based on percentage of cycles delivered, were rash (68%), hypomagnesemia (51%), anemia (29%), fatigue (23%), lymphopenia (23%), and dry skin (21%). Adverse events of grade 3 or worse were rare; the most frequent were fatigue and lymphopenia, seen in 3% of treatment cycles.

Efficacy

Efficacy data for the phase II cohort are summarized in Table 3. A total of 238 treatment cycles (median, 4; range, 1 to 15) were administered to 44 patients. Nine patients achieved an objective tumor response, confirmed by independent radiology review. One patient had a complete response and remained on study treatment for 15 cycles before disease progression. Eight patients had partial responses lasting seven to 12 cycles. The objective response rate, by intention-to-treat status, was nine of 43 (21%; 95% CI, 10% to 36%). Twenty-one patients achieved disease stabilization, two of whom had unconfirmed partial responses. The rate of stable disease was 21 of 43 (49%; 95% CI, 33% to 65%) by intention-to-treat status. Nine patients had disease progression as their best response on study.

All patients who discontinued study treatment did so because of disease progression or death except one patient who withdrew consent (after 2 weeks) and two patients who discontinued study treatment due to adverse events (after 2 and 14.9 weeks, respectively). Median PFS was 3.3 months (95% CI, 2.7 to 4.8 months), and the 6-month PFS rate was 20.6% (95% CI, 11.2% to 38.0%; Fig 1A). All but four patients (one withdrew consent at 2 weeks, one was lost to follow-up with brain metastases at 1 month, and two are alive at 15.8 and 18.5 months, respectively) are known to have died. Median OS was 7.9

Table 2. Most Frequent Adverse Events at Least Possibly Related to Study Therapy (phase II cohort)

Adverse Event	All Grades		All Grades		Grades 3, 4, 5	
	No. of Patients	%	No. of Cycles	%	No. of Cycles	%
Total	44	100	238	100	238	100
Rash/desquamation	31	70	163	68	0	0
Hypomagnesemia	26	59	122	51	4	2
Anemia	16	36	68	29	0	0
Fatigue	18	41	54	23	7	3
Lymphopenia	13	30	54	23	7	3
Dry skin	9	20	50	21	0	0
Dry mouth	5	11	33	14	0	0
Hypoalbuminemia	14	32	31	13	0	0
Creatinine	9	20	30	13	2	1
Nausea	12	27	29	12	2	1
Diarrhea	14	32	26	11	2	1
Hypokalemia	8	18	26	11	5	2
Hyponatremia	9	20	25	11	1	0.4
Hyperkalemia	5	11	20	8	1	0.4
Alkaline phosphatase	9	20	19	8	0	0
Leukopenia	12	27	18	8	0	0
Anorexia	4	9	16	7	2	1
Hypocalcemia	8	18	16	7	0	0
AST	9	20	15	6	0	0
ALT	7	16	14	6	0	0

Table 3. Summary of Efficacy Data (phase II cohort)

Efficacy Parameter	Intention-to-Treat Status (n = 43) No. of Patients	%	95% CI	Assessable Patients Only (n = 39) No. of Patients	%
Best response					
Complete response	1	3		1	3
Partial response	8	19		8	21
Stable disease*	21	49		21	54
Progressive disease	9	21		9	23
Not assessable	4	9		—	
Progression-free survival, months					
Median	3.3		2.7 to 4.8		
6-month rate		20.6	11.1 to 38.0		
Overall survival, months					
Median	7.9		5.6 to 9.5		
6-month rate		61.0	47.7 to 77.9		

*Includes two patients with unconfirmed partial responses.

months (95% CI, 5.6 to 9.5 months), 6-month OS rate was 61.0% (95% CI, 47.7% to 77.9%), and 12-month OS rate was 19.5% (95% CI, 10.5% to 36.3%; Fig 1B).

Subgroup Analysis

When analyzed as a function of rash severity in cycle 1, the median survival durations of patients with no rash, grade 1 rash, and grade 2 rash were 4.2, 7.9, and 9.2 months, respectively ($P = .034$). No patients developed skin rashes of grade 3 or worse intensity. Figure 1C illustrates the Kaplan-Meier curves of survival as stratified by grade of skin rash in cycle 1.

Pharmacokinetic Analysis

$C_{ss,min}$ of erlotinib and its metabolite OSI-420 were measured on days 1, 15, 22, and 43 for patients who received erlotinib at 150 mg PO daily (dose levels 2 and 3) and erlotinib at 100 mg PO daily (phase II cohort including patients who received the RPTD in the phase I component). These results are summarized in Table 4. Of note, the erlotinib $C_{ss,min}$ values of patients treated at both the 100- and 150-mg dose levels exceeded 500 ng/mL, the target plasma concentration for EGFR inhibition that is associated with antiproliferative activity in preclinical studies.[15]

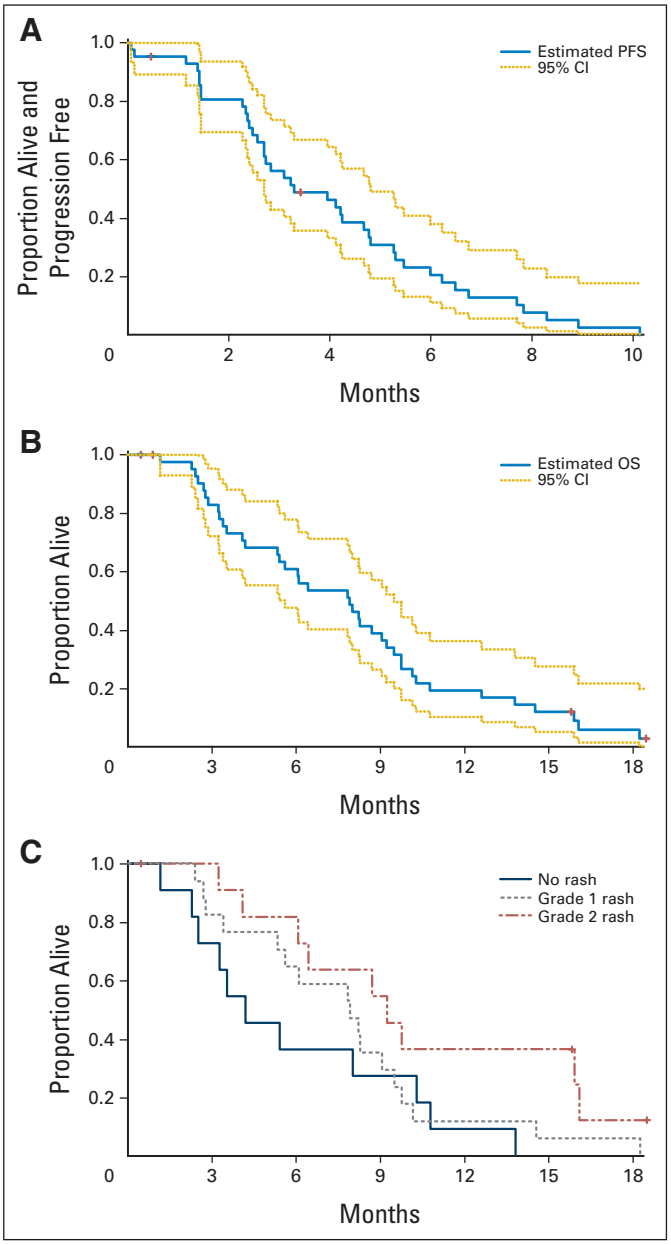

Fig 1. (A) Progression-free survival (PFS) for phase II cohort. (B) Overall survival for phase II cohort. (C) Overall survival stratified by grade of skin rash in cycle 1.

DISCUSSION

The RPTD derived from the dose-finding component of this study was erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV every 3 weeks. Objective tumor responses were seen in nine of 39 assessable patients, which included one complete and eight partial responses. Two additional patients had unconfirmed partial responses that were counted as stable disease. The study's preset criterion, which was calculated based on a *P*0 of .2 and *P*1 of .4, specified that this regimen would be considered for additional evaluation if 11 or more objective responses were observed out of 37 assessable patients. With this fairly ambitious threshold, the efficacy outcome of this study did not fulfill its preset criterion. However, the expectation to obtain response rates near 40% with a targeted agent plus platinum combination in recurrent or metastatic HNSCC is likely unrealistic.

The results of this study are consistent with those published in the literature. Table 5 summarizes the results of antitumor activity of EGFR inhibitors with or without platinum in patients with recurrent or metastatic HNSCC.[9,16-20] Single-agent EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, exhibit objective response rates in the range of 1% to 10%, and disease stabilization rates of 33% to 47%.[9,19,20] PFS ranged from 1.8 to 3.4 months and median survival ranged from 5.5 to 8.1 months. Patients in these studies typically were heavily pretreated, with 59% to 85% having had prior exposure to chemotherapy. The combination of the anti-EGFR monoclonal antibody, cetuximab, with cisplatin has been evaluated in both platinum-sensitive and platinum-refractory recurrent or metastatic HNSCC populations.

Table 4. Steady-State Plasma Concentrations of Erlotinib and OSI-420

Drug	Erlotinib Dose (mg)	Steady-State Plasma Concentration (ng/mL)											
		Day 1			Day 15			Day 22			Day 43		
		Mean	Standard Deviation	No. of Patients	Mean	Standard Deviation	No. of Patients	Mean	Standard Deviation	No. of Patients	Mean	Standard Deviation	No. of Patients
Erlotinib	100	1,292	939	41	1,371	1,334	13	1,310	1,099	27	986	606	24
	150	2,899	1,568	6	1,272	513	4	1,535	731	5	1,220	868	3
OSI-420	100	147	148	41	164	176	13	171	192	26	88	55	24
	150	325	225	6	116	47	4	151	101	5	126	120	3

In the studies that evaluated this combination among patients with platinum-refractory disease,[17,18] objective response rates and disease stabilization rates generally were approximately 6% to 20% and 44% to 53%, respectively. PFS durations varied from 2.0 to 3.0 months and median survival varied from 4.3 to 6.1 months. These results are remarkably similar to those obtained using single-agent tyrosine kinase inhibitors. Burtness et al[16] presented the only phase III data of cetuximab plus cisplatin versus placebo plus cisplatin in patients with platinum-sensitive recurrent or metastatic HNSCC. In that study, the addition of cetuximab to cisplatin significantly increased objective response rate, but did not significantly improve PFS and OS. Results from our phase II study of erlotinib plus cisplatin are highly concordant with those derived from the cetuximab plus cisplatin arm of the randomized phase III trial, with response rates of 21% *v* 26%, PFS of 3.3 *v* 4.2 months, and median survival of 7.9 *v* 9.2 months, respectively.

It is unlikely that the combination of erlotinib and cisplatin will yield improved survival outcomes compared with cisplatin alone, given the results of the phase III trial evaluating cetuximab plus cisplatin.[16] However, among patients who are symptomatic (in whom it is important to achieve rapid tumor shrinkage or disease stabilization), the erlotinib plus cisplatin combination offers a disease control rate of 70%, with minimal adverse effects. When compared against standard regimens using infusional fluorouracil or higher dose cisplatin (100 mg/m^2), the combination of erlotinib and cisplatin (75 mg/m^2) may obviate the need for prolonged continuous intravenous infusions or overnight admissions for hydration. The therapeutic index of the erlotinib and cisplatin combination in the current study compares favorably to standard cytotoxic platinum-based doublets, especially with respect to its efficacy outcomes and its low incidences of grade 3 or worse adverse events.[2]

Similar to previous studies with EGFR inhibitors,[9,16,17,20] our study showed in subgroup analysis that the development of skin rash correlated with survival outcomes in this patient population, and not with tumor response. The early development of skin rash, along with pharmacodynamic markers in tumor and skin biopsies, reported in our companion article,[12] require additional validation of their predictive roles in clinical outcome.

The concurrent administration schedule of erlotinib and cisplatin in this study is a subject worthy of discussion. Preclinically in head and neck tumor xenografts, regardless of the dosing sequence (ie, erlotinib before cisplatin, cisplatin before erlotinib, or concurrent delivery of both agents), no differences in antitumor activity or toxicity was seen.[11] Clinical studies of concurrent administration

Table 5. Comparison of Intention-to-Treat Antitumor Activity of EGFR Inhibitors in Recurrent or Metastatic HNSCC

Study	Phase	No. of Patients	CR + PR (%)	SD (%)	PFS (months)	MS (months)
EGFR inhibitor + platinum combination						
Cetuximab + cisplatin[16]	III	57	26	NR	4.2	9.2
Placebo + cisplatin[16]		60	10	NR	2.7	8.0
Cetuximab + cisplatin[17]	II	96*	10	43	2.8†	6.0†
Cetuximab + cisplatin[18]	II	51‡	18	59	4.9	11.7
		25§	20	44	3.0	6.1
		54‖	6	46	2.0	4.3
Erlotinib + cisplatin (current study)	II	43	21	49	3.3	7.9
EGFR inhibitor single agent						
Gefitinib 250 mg[19]	II	70	1.4	33	1.8	5.5
Gefitinib 500 mg[20]	II	52	11	43	3.4	8.1
Erlotinib[9]	II	115	4.3	38	2.2¶	6.0

Abbreviations: EGFR, epidermal growth factor receptor; HNSCC, squamous cell carcinoma of the head and neck; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; MS, median survival; NR, not reported.
*Patients were platinum refractory.
†Converted from days to months.
‡Patients who had stable disease while receiving platinum-based therapy.
§Patients who had progressive disease while receiving platinum-based therapy.
‖Patients who developed progressive disease within 90 days after platinum-based therapy.
¶Converted from weeks to months.

of erlotinib and platinum-based chemotherapy in advanced non–small-cell lung cancer have failed to demonstrate benefits in response rates or survival compared with chemotherapy alone.[21,22] Whether this lack of benefits is due to negative pharmacologic or molecular interactions is uncertain, although speculations about the potential mechanisms have been raised.[23] Equally unclear is the relevance of this finding to the combination of EGFR tyrosine kinase inhibitors and platinum-based chemotherapy in other disease sites, such as HNSCC. Although the lack of survival advantage with cetuximab plus cisplatin versus placebo plus cisplatin in the randomized trial by Burtness et al[16] raised similar concerns, this study was not powered to detect OS differences as its primary end point.

In conclusion, even though this trial did not meet its preset criterion for additional development of the erlotinib plus cisplatin combination in recurrent or metastatic HNSCC, this regimen was well tolerated and convenient in its delivery.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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