Erlotinib in Previously Treated Non–Small-Cell Lung Cancer

Frances A. Shepherd, M.D., José Rodrigues Pereira, M.D., Tudor Ciuleanu, M.D., Eng Huat Tan, M.D.,
Vera Hirsh, M.D., Sumitra Thongprasert, M.D., Daniel Campos, M.D., Savitree Maoleekoonpiroj, M.D.,
Michael Smylie, M.B., Ch.B., Renato Martins, M.D., Maximiliano van Kooten, M.D., Mircea Dediu, M.D.,
Brian Findlay, M.D., Dongsheng Tu, Ph.D., Dianne Johnston, Andrea Bezjak, M.D., Gary Clark, Ph.D.,
Pedro Santabárbara, M.D., Ph.D., and Lesley Seymour, M.D., Ph.D.,
for the National Cancer Institute of Canada Clinical Trials Group*

ABSTRACT

BACKGROUND

We conducted a randomized, placebo-controlled, double-blind trial to determine whether the epidermal growth factor receptor inhibitor erlotinib prolongs survival in non–small-cell lung cancer after the failure of first-line or second-line chemotherapy.

METHODS

Patients with stage IIIB or IV non–small-cell lung cancer, with performance status from 0 to 3, were eligible if they had received one or two prior chemotherapy regimens. The patients were stratified according to center, performance status, response to prior chemotherapy, number of prior regimens, and prior platinum-based therapy and were randomly assigned in a 2:1 ratio to receive oral erlotinib, at a dose of 150 mg daily, or placebo.

RESULTS

The median age of the 731 patients who underwent randomization was 61.4 years; 49 percent had received two prior chemotherapy regimens, and 93 percent had received platinum-based chemotherapy. The response rate was 8.9 percent in the erlotinib group and less than 1 percent in the placebo group (P<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (hazard ratio, 0.61, adjusted for stratification categories; P<0.001). Overall survival was 6.7 months and 4.7 months, respectively (hazard ratio, 0.70; P<0.001), in favor of erlotinib. Five percent of patients discontinued erlotinib because of toxic effects.

CONCLUSIONS

Erlotinib can prolong survival in patients with non–small-cell lung cancer after first-line or second-line chemotherapy.

L UNG CANCER IS THE LEADING CAUSE OF cancer death among men and women in North America.[1] In advanced non–small-cell lung cancer, chemotherapy offers symptomatic relief and modest improvement in survival[2]; responses are brief, with a median time to progression of three to five months. Second-line chemotherapy with docetaxel can prolong survival after platinum-based therapy for non–small-cell lung cancer.[3,4] However, there is at present no defined role for third-line chemotherapy. The futility of offering third-line chemotherapy was demonstrated by Massarelli et al.,[5] who reported a response rate of only 2 percent and a median survival of four months. Shepherd et al.[6] showed that among patients treated with docetaxel after the failure of two or more chemotherapy regimens, survival was identical to that among patients treated with supportive care.

The epidermal growth factor receptor (EGFR) family is part of a complex signal-transduction network that is central to several critical cellular processes. Since EGFR is often found in non–small-cell lung cancer cells,[7,8] it has been the focus of efforts to develop new agents that target the EGFR pathway. Erlotinib (Tarceva, OSI Pharmaceuticals) and gefitinib (Iressa, AstraZeneca) inhibit the tyrosine kinase activity of EGFR and have been studied extensively.[9-12] In randomized phase 2 trials of gefitinib (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL] 1 and 2),[10,11] the tumors of 10 to 20 percent of patients who were previously treated with platinum-based regimens responded, and in a phase 2 trial of erlotinib among previously treated patients with non–small-cell lung cancer in which 10 percent or more of the cells expressed EGFR, the response rate was 12.3 percent.[12] These promising rates are perhaps higher than those possible with other forms of chemotherapy,[3-6] but it is unknown whether treatment with an EGFR inhibitor prolongs survival. For this reason, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) conducted a trial (BR.21) to compare erlotinib with placebo after the failure of standard chemotherapy for non–small-cell lung cancer. The inclusion of a control group receiving placebo was considered ethical in view of the lack of benefit from further chemotherapy after the failure of standard treatment.[5,6]

METHODS

STUDY DESIGN

This international, phase 3, randomized, double-blind, placebo-controlled trial of erlotinib after the failure of first-line or second-line chemotherapy for non–small-cell lung cancer was designed by the NCIC CTG. Patients were randomly assigned in a 2:1 ratio to receive oral erlotinib at a dose of 150 mg daily or placebo. Randomization was performed centrally by Applied Logic Associates (Houston), with the use of the minimization method.[13] Patients were stratified according to center, Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2 or 3, with higher scores indicating greater impairment), best response to prior therapy (complete or partial response vs. stable disease vs. progressive disease), number of prior regimens received (one vs. two), and exposure to prior platinum therapy (yes vs. no).

The primary end point was overall survival. Secondary end points included progression-free survival, overall response rate (complete and partial), duration of response, toxic effects, and quality of life. Responses were assessed with the use of the Response Evaluation Criteria in Solid Tumors (RECIST),[14] and toxic effects were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0). The European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) and the quality-of-life questionnaire for patients with lung cancer (QLQ-LC13) were used to evaluate patients' quality of life.

The protocol was approved by the ethics review boards at all participating institutions, and all patients provided written informed consent. Support was provided by the NCIC and OSI Pharmaceuticals. Data were collected, managed, and analyzed by the NCIC CTG, and the manuscript was written by members of the NCIC CTG. OSI Pharmaceuticals reviewed the final manuscript and provided comments on it. Confidentiality was maintained by both the NCIC CTG and OSI Pharmaceuticals. The study chair, Dr. Shepherd, and the physician coordinator, Dr. Seymour, reviewed all the data and confirmed their completeness and accuracy.

ELIGIBILITY CRITERIA

Patients 18 years of age or older with an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 3 were eligible in the presence of documented pathological evidence of non–small-cell lung cancer. The patients had to have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy. Patients 70 years of age or older may have received therapy with one or two single agents. Patients had to have recovered from any toxic effects of therapy and were randomly assigned to the study treatment at least 21 days after chemotherapy (14 days after treatment with vinca alkaloids or gemcitabine) and 7 days after radiation. Adequate hematologic and biochemical values were required.

Patients with prior breast cancer, melanoma, or hypernephroma were ineligible, as were those with other malignant diseases (except basal-cell skin cancers) within the preceding five years. Other exclusion criteria were symptomatic brain metastases, clinically significant cardiac disease within one year, ventricular arrhythmias requiring medication, and clinically significant ophthalmologic or gastrointestinal abnormalities.

STUDY PROCEDURES

Within seven days before randomization, a history and physical examination were obtained and hematologic and biochemical testing, chest radiography, and assessments of toxic effects and quality of life were obtained. Computed tomographic scans of the chest and abdomen were obtained within 28 days before randomization. For a patient to be evaluated for a response, at least one measurable lesion was required, but measurable disease was not mandatory for eligibility. Only patients with measurable disease were included in the analyses of complete or partial response.

Administration of the study medication was to start within two days after randomization. For grade 2 diarrhea, loperamide was recommended without reduction of the dose of erlotinib. For grade 3 diarrhea, the study treatment was withheld until the diarrhea was grade 1 or less, and then erlotinib at a dose of 100 mg daily was started. For grade 1 or 2 rash, treatment modification was not recommended. For grade 3 rash, treatment was withheld, the rash was treated symptomatically, and erlotinib at a dose of 100 mg daily was restarted when the rash was grade 1 or less.

History taking, physical examination, and hematologic and biochemical testing were performed every four weeks, and radiologic investigations every eight weeks. Patients' quality of life was evaluated every four weeks in countries with validated versions of the questionnaires.

EGFR EXPRESSION

Separate written consent for optional tissue banking and correlative studies was obtained. EGFR expression was determined with the use of immunohistochemistry in a central laboratory that used Dako kits (DakoCytomation). Positivity was defined as more than 10 percent of cells staining at any intensity for EGFR.

STATISTICAL ANALYSIS

The trial was designed to detect, with 90 percent power and a two-sided type I error of 5 percent, a 33 percent improvement in median survival from four months as estimated in the placebo group. For the final analysis, 582 deaths were required and were projected to occur with a sample size of 700 patients enrolled over a period of 14 months with 6 months of follow-up. The required number of deaths had occurred by January 2004, and the database was locked as of April 23, 2004. There was no interim analysis. Tumor responses were validated centrally for the first 333 patients in the trial.

The stratified log-rank test, accounting for stratification factors at randomization (except center) and EGFR protein expression (positive vs. negative vs. unknown), was used to compare progression-free survival and overall survival between treatment groups. Exploratory forward stepwise regression analyses with the use of the Cox model were performed to adjust for treatment effect and to identify prognostic factors for progression-free survival and overall survival. Candidate covariates included EGFR expression, stratification factors (except center), sex, age (60 years or less vs. more than 60 years), race or ethnic group (Asian vs. others), prior radiotherapy (yes vs. no), histologic subtype of cancer (adenocarcinoma vs. others), and smoking status (smoker vs. nonsmoker vs. unknown). Race was self-reported or determined by study personnel and was not based on country of domicile. Fisher's exact test was used to compare response rates between levels of potential predictors and rates of toxic effects between treatments. Times to deterioration (a 10-point increase from the baseline score) for

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Erlotinib (N=488)	Placebo (N=243)
Age (yr)		
Median	62	59
Range	34–87	32–89
<60 (% of patients)	42.6	51.0
≥60 (% of patients)	57.4	49.0
Sex (% of patients)		
Male	64.5	65.8
Female	35.5	34.2
Race or ethnic group (% of patients)†		
Asian	12.9	12.2
Other	87.1	87.8
Performance status (% of patients)‡		
0	13.1	14.0
1	52.5	54.3
2	25.8	23.0
3	8.6	8.6
Weight loss >10% (% of patients)	11.0	12.0
Pathological subtype (% of patients)		
Adenocarcinoma	50.4	49.0
Squamous-cell carcinoma	29.5	32.1
Other	20.1	18.9
Prior chemotherapy (% of patients)		
One regimen	50.6	50.2
Two or more regimens	49.4	49.8
Platinum-based therapy	92.0	91.8
Response to prior chemotherapy (% of patients)		
Complete or partial response	38.1	37.9
Stable disease	34.0	34.2
Progressive disease	27.9	28.0
Smoking status (% of patients)		
Current smoker or ever smoked	73.4	77.0
Never smoked	21.3	17.3
Unknown	5.3	5.8
EGFR protein expression (% of patients)§		
Positive	24.0	27.6
Negative	19.1	19.8
Unknown	56.9	52.6

* Because of rounding, not all percentages sum to 100.
† Race or ethnic group was self-reported or determined by study personnel and was not based on country of domicile.
‡ A higher score indicates greater impairment.
§ Epidermal growth factor receptor (EGFR) expression was assessed by immunohistochemistry.

cough, dyspnea, and pain were identified prospectively as the primary end points for the analysis of quality of life[15] and were analyzed with the use of the log-rank test, with adjustment according to the Hochberg method[16] for the comparison of multiple end points. All P values were two-sided.

RESULTS

PATIENT CHARACTERISTICS

Between August 2001 and January 2003, 731 patients were randomly assigned to erlotinib (488) or placebo (243). Twenty-two patients (12 assigned to erlotinib and 10 assigned to placebo) were ineligible for the following reasons: three prior chemotherapy regimens (9); single-agent chemotherapy for patients less than 70 years of age (2); inadequate time since the last treatment (5); abnormal biochemistry results (4); and symptomatic brain metastases (2). All 731 patients were included in the efficacy analyses, and 727 treated patients (485 assigned to erlotinib and 242 assigned to placebo) were included in the safety analyses. Eight patients assigned to erlotinib (1.6 percent) and 18 assigned to placebo (7.4 percent) received other EGFR inhibitors after study medication was discontinued. The groups were balanced with respect to baseline characteristics and important prognostic variables (Table 1).

RESPONSE AND SURVIVAL

In patients with at least one target lesion, the lesions were evaluated according to RECIST (427 patients assigned to erlotinib and 211 assigned to placebo). In the erlotinib group, the rates of complete response and partial response were 0.7 percent and 8.2 percent, respectively (median duration, 7.9 months); in the placebo group, the rate of partial response was less than 1 percent (P<0.001), but these responses were not externally validated. In an intention-to-treat analysis of all patients randomly assigned to treatment, the disease-control rate (i.e., the rate of complete or partial responses and stable disease) in the erlotinib group was 45 percent; 38 percent of the patients had progressive disease, and among the remaining 17 percent progression was not confirmed. The likelihood of a response to erlotinib (Table 2) among patients with non–small-cell lung cancer was not significantly altered by performance status, prior treatments, prior response, or age, but it was higher among women (P=0.006), nonsmokers (P<0.001), Asians

(P=0.02), patients with adenocarcinoma (P<0.001), and patients in whom 10 percent or more of the tumor cells expressed EGFR (P=0.10). In multiple logistic-regression analyses, never having smoked (P<0.001), the presence of adenocarcinoma (P=0.01), and EGFR expression (P=0.03) were associated with responsiveness to erlotinib.

At the time of analysis, 587 deaths had occurred (378 in the erlotinib group and 209 in the placebo group). Figure 1 shows Kaplan–Meier curves for overall survival and progression-free survival. Median overall survival in the erlotinib group was 6.7 months, and in the placebo group it was 4.7 months (adjusted hazard ratio, 0.70; 95 percent confidence interval, 0.58 to 0.85; P<0.001). In the Cox regression analysis, erlotinib remained associated with longer survival (P=0.002), as did Asian origin (P=0.01), adenocarcinoma on histologic examination (P=0.004), and never having smoked (P=0.048 vs. current or past smoking). Table 3 shows the exploratory subgroup analyses. Although the sample sizes may be inadequate to detect small or moderate differences, a benefit from erlotinib was apparent in most of the subgroups. The interaction between treatment and the covariate defining the subgroup was statistically significant only for smoking status. At the time of analysis, 682 patients had had progression of disease (450 in the erlotinib group and 232 in the placebo group). Median progression-free survival was 2.2 months in the erlotinib group and 1.8 months in the placebo group (adjusted hazard ratio, 0.61; 95 percent confidence interval, 0.51 to 0.74; P<0.001). In the Cox model, treatment with erlotinib (P<0.001) and never having smoked (P<0.01 for the comparison with current or past smoking) were associated with longer progression-free survival.
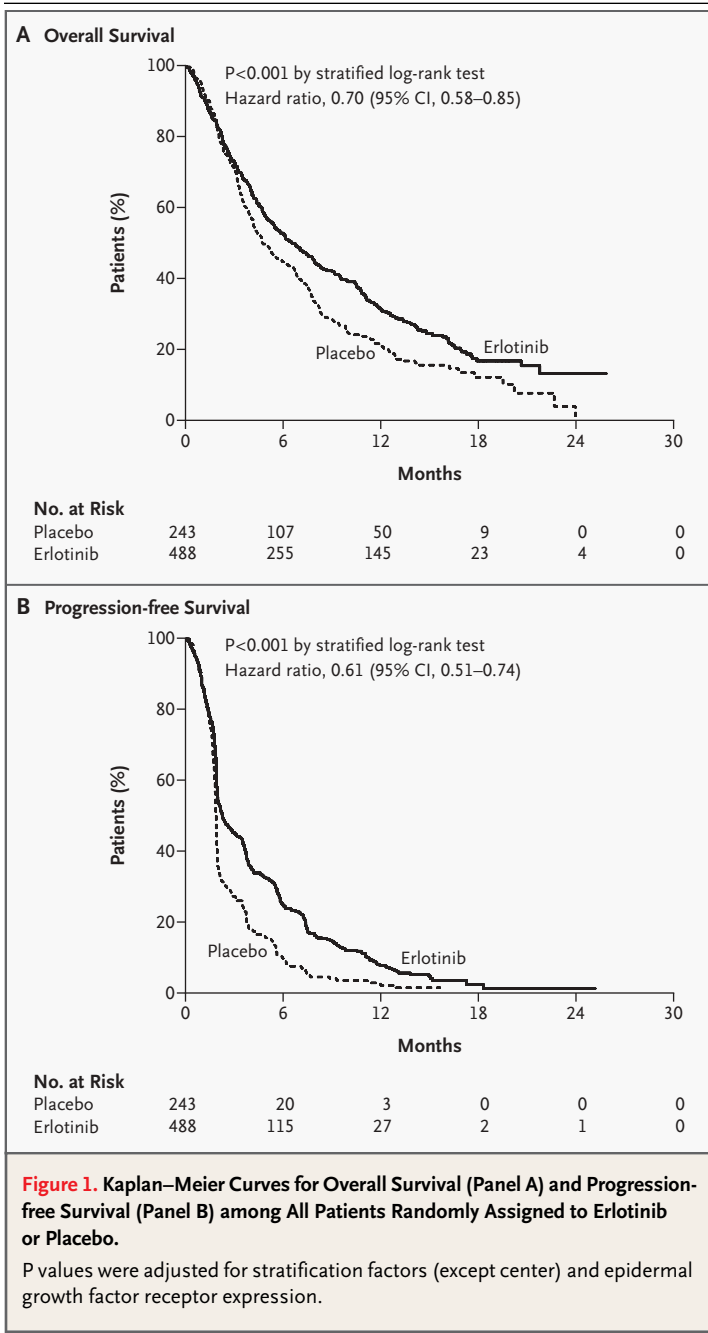
TOXIC EFFECTS

Four patients who underwent randomization did not receive treatment. Table 4 shows that 19 percent of the erlotinib group required dose reductions because of drug-related toxic effects, as compared with 2 percent of the placebo group, most frequently because of rash (12 percent) and diarrhea (5 percent); 26 patients (5 percent) discontinued erlotinib because of drug-related toxic effects, as compared with 4 patients (2 percent) receiving placebo. There was a higher incidence of infection among the erlotinib patients, which may reflect longer follow-up (P<0.001). There were similar rates of pneumonitis and pulmonary fibrosis in the two groups.

Table 2. Analysis of Responses to the Study Treatment.*

Factor	No. of Cases Evaluated	No. of Responses (Complete and Partial)	Overall Response Rate (%)	P Value
Treatment				
Erlotinib	427	38	8.9	<0.001
Placebo	211	2	<1	
Age				
<60 yr	177	19	10.7	0.30
≥60 yr	250	19	7.6	
Sex				
Male	281	17	6.0	0.006
Female	146	21	14.4	
Pathological subtype				
Adenocarcinoma	209	29	13.9	<0.001
Other	218	9	4.1	
Performance status				
0 or 1	274	21	7.7	0.29
2 or 3	153	17	11.1	
Response to prior therapy				
Complete and partial responses	174	13	7.5	0.65
Progressive disease	87	9	10.3	
Stable disease	166	16	9.6	
Prior regimens				
1	214	19	8.9	1.00
2 or 3	213	19	8.9	
Prior platinum-based therapy				
Yes	396	36	9.1	1.00
No	31	2	6.5	
EGFR expression†				
Positive	106	12	11.3	0.10
Negative	80	3	3.8	
Unknown	241	23	9.5	
Smoking status				
Current smoker or ever smoked	311	12	3.9	<0.001
Never smoked	93	23	24.7	
Unknown	23	3	13.0	
Race or ethnic group				
Asian	53	10	18.9	0.02
Other	374	28	7.5	

* Responses were assessed according to the Response Evaluation Criteria in Solid Tumors in patients with one or more confirmed lesions and at least one follow-up radiologic examination.
† Epidermal growth factor receptor (EGFR) expression was assessed by immunohistochemistry.

A Overall Survival

P<0.001 by stratified log-rank test
Hazard ratio, 0.70 (95% CI, 0.58–0.85)

No. at Risk					
Placebo	243	107	50	9	0	0
Erlotinib	488	255	145	23	4	0

B Progression-free Survival

P<0.001 by stratified log-rank test
Hazard ratio, 0.61 (95% CI, 0.51–0.74)

No. at Risk					
Placebo	243	20	3	0	0	0
Erlotinib	488	115	27	2	1	0

Figure 1. Kaplan–Meier Curves for Overall Survival (Panel A) and Progression-free Survival (Panel B) among All Patients Randomly Assigned to Erlotinib or Placebo.

P values were adjusted for stratification factors (except center) and epidermal growth factor receptor expression.

among patients receiving erlotinib and 3.7 months among those receiving placebo, P=0.04 with Hochberg adjustment), dyspnea (4.7 months and 2.9 months, respectively; adjusted P=0.03), and pain (2.8 months and 1.9 months, respectively; adjusted P=0.04) in favor of erlotinib. These results are consistent with response-based analyses of the quality of life, which found that more patients receiving erlotinib had improvement in cough, pain, and dyspnea and in the domain of overall physical function (further information is in the Supplementary Appendix, available with the complete text of this article at www.nejm.org).

DISCUSSION

Docetaxel is the only agent known to prolong survival among patients with disease progression after cisplatin-based chemotherapy for non–small-cell lung cancer.[3,4,17] Few options are available for the treatment of patients with disease progression after docetaxel or those who are not eligible for second-line chemotherapy.[5,6] Clearly, new treatments are needed for such patients.

Expression of EGFR is common in non–small-cell lung cancer.[18-20] Several agents that target EGFR are in various phases of clinical evaluation.[9,21] The orally active EGFR tyrosine kinase inhibitors gefitinib and erlotinib have been evaluated in several trials. In the IDEAL 1 trial,[10] patients with non–small-cell lung cancer with disease progression after platinum-based chemotherapy were randomly assigned to receive gefitinib, at a dose of 250 mg or 500 mg daily. There were no differences between the two doses with respect to response rate, time to progression, or median survival. The response rates were also similar whether gefitinib was used as second-line treatment (17.9 percent of patients) or third-line treatment (19.8 percent of patients). In the IDEAL 2 trial,[11] which enrolled symptomatic patients in whom two or more chemotherapy regimens containing platinum and docetaxel had failed, the response rates were 12 percent and 9 percent, respectively, for the two dose levels. More adverse events were seen with the dose of 500 mg in both trials, but discontinuation of treatment because of toxic effects was uncommon at either dose. In a phase 2 trial of erlotinib, the response rate was 12 percent, and response did not correlate with level of EGFR in the tumor.[12]

In our trial, the response rate of 8.9 percent was similar to rates reported for erlotinib and ge-

Two patients died of pneumonitis (one in each group).

QUALITY OF LIFE

Compliance was similar in the two groups. Patients who had responded to the quality-of-life questionnaire at baseline and had one follow-up assessment were included in the analysis. The median time to deterioration with regard to cough (4.9 months

Table 3. Analysis of Survival.*

Factor	No. of Patients	Univariate Hazard Ratio (95% CI)†	P Value	Multivariate Hazard Ratio (CI)‡	P Value§
Treatment group					
Erlotinib	488	0.7 (0.6–0.9)	<0.001	0.7 (0.6–0.9)	0.002
Placebo	243				
Age				NI	
<60 yr	332	0.8 (0.6–1.0)	0.04		
≥60 yr	399	0.8 (0.6–1.0)	0.02		
Sex				NI	
Male	475	0.8 (0.6–0.9)	0.01		
Female	256	0.8 (0.6–1.1)	0.13		
Pathological subtype					
Adenocarcinoma	365	0.7 (0.6–0.9)	0.008	0.8 (0.6–0.9)	0.004
Other	366	0.8 (0.6–1.0)	0.07		
Performance status				NA	
0 or 1	486	0.7 (0.6–0.9)	0.003		
2	182	0.8 (0.5–1.1)	0.11		
3	63	0.8 (0.4–1.3)	0.33		
Response to prior therapy				NA	
Complete response or partial response	292	0.7 (0.5–0.9)	0.004		
Stable disease	287	0.8 (0.6–1.1)	0.18		
Progressive disease	152	0.9 (0.6–1.2)	0.34		
Prior regimens				NA	
1	369	0.8 (0.6–1.1)	0.03		
2 or 3	362	0.8 (0.6–1.1)	0.02		
Prior platinum-based therapy				NA	
Yes	672	0.7 (0.6–0.9)	<0.001		
No	59	1.7 (0.7–2.7)	0.30		
EGFR expression				NA	
Positive	184	0.7 (0.5–0.9)	0.02		
Negative	141	0.9 (0.6–1.4)	0.70		
Unknown	406	0.8 (0.6–1.0)	0.03		
Smoking status					
Current smoker or ever smoked	545	0.9 (0.7–1.0)	0.14	Reference group	
Never smoked	146	0.4 (0.3–0.6)	<0.001	0.8 (0.6–1.0)	0.048
Unknown	40	1.1 (0.5–2.6)	0.80	1.0 (0.7–1.5)	0.89
Race or ethnic group					
Asian	91	0.6 (0.4–1.0)	0.06	0.7 (0.5–0.9)	0.01
Other	640	0.8 (0.7–0.9)	0.01		

* CI denotes confidence interval, NI not included in the final model, and NA not applicable as a stratification factor.
† The univariate hazard ratio was derived from a Cox model with a single treatment covariate.
‡ The hazard ratio between levels of respective covariates was derived from the final stratified Cox regression model.
§ P values are for the comparison of patients who had never smoked and those whose history of smoking was unknown with those who were smokers.

Table 4. Toxic Effects and Dose Modifications among 727 Patients Receiving the Study Drugs.

Toxic Effect	Erlotinib (N=485)		Placebo (N=242)		P Value	
	All	Grades 3 to 5	All	Grades 3 to 5	All	Grades 3 to 5
			percent			
Rash	76	9	17	0	<0.001	<0.001
Anorexia	69	9	56	5	<0.001	0.06
Nausea	40	3	34	<1	0.12	0.07
Vomiting	25	3	23	2	0.52	0.45
Stomatitis	19	<1	3	0	<0.001	0.31
Diarrhea	55	6	19	<1	<0.001	<0.001
Dehydration	7	4	6	3	0.64	0.67
Ocular toxic effect	28	1	9	<1	<0.001	0.67
Fatigue	79	19	74	23	0.22	0.33
Infection	34	2	21	5	<0.001	0.03
Pulmonary fibrosis	3	<1	3	0	1.0	1.0
Pneumonitis or pulmonary infiltrates*	3	<1	3	<1	0.64	1.0
Death from pneumonitis	1 patient		1 patient			
Reason for dose reduction						
Any toxic effect	19		2		<0.001	
Diarrhea	5		0		<0.001	
Rash	12		0		<0.001	
Conjunctivitis	1		0		0.19	
Vomiting	1		0		0.55	
Stomatitis	<1		0		1.0	
Reason for treatment interruption						
Any toxic effect	27		5		<0.001	
Diarrhea	6		<1			
Rash	14		0		<0.001	
Conjunctivitis	1		0		0.19	
Vomiting	2		<1		0.11	
Stomatitis	<1		<1		1.0	
Treatment discontinued because of any toxic effect	5		2		0.02	

* All cases designated "pneumonitis" were reviewed by a study physician. Cases of "pneumonia" were also reviewed and reclassified as pneumonitis, if appropriate.

fitinib.[10-12] Some investigators have reported that responsiveness to EGFR inhibitors correlates with sex, histologic type, race or ethnic origin, and smoking status.[10,11,21] We also found that response was higher among Asians, women, patients with adenocarcinoma, and lifetime nonsmokers. Contrary to previous reports,[12] the response rate in our trial was higher when 10 percent or more of tumor cells expressed EGFR.

Activating mutations in the *EGFR* gene have been found to predict a response to gefitinib.[22-27] The results of our assays for the number of copies and mutation status of the *EGFR* gene are published in this issue of the *Journal*.[28] Higher response rates were found among patients with high numbers of gene copies and mutations, but the difference was significant only for gene copies.

Because none of the early trials[10-12] had a placebo control group, it is not possible to determine whether EGFR-inhibitor therapy was superior to

palliative treatment. In our placebo-controlled trial, erlotinib did provide clinically meaningful prolongation of survival. According to the Kaplan–Meier estimates, the median survival was prolonged by two months, and 31 percent of patients treated with erlotinib were alive at one year, as compared with 22 percent in the placebo group. The two-month prolongation of survival is similar to that achieved with docetaxel in the setting of second-line chemotherapy,[3,4] even though half the patients in our trial were treated after both first-line and second-line chemotherapy. In this trial and another trial,[3] a significant prolongation of survival was achieved despite response rates of less than 10 percent, perhaps because a high proportion of the patients had durable stable disease while receiving treatment. Survival in this trial appears to be longer than what was achieved in a similar trial of gefitinib, although the response rates were similar in both studies. The characteristics of the patients in these two trials, however, may have differed somewhat.[29]

Exploratory multivariate analyses showed that only Asian origin, adenocarcinoma on histologic examination, and a history of not smoking were significant independent predictors of survival after adjustment for treatment and other potential predictors. Erlotinib had a beneficial effect on survival in almost all subgroups tested, but only the interaction between smoking status and treatment was significantly predictive of a differential effect on survival. Notably, the presence of *EGFR* gene mutations was not predictive of a survival benefit from erlotinib in our study.[28]

In the IDEAL 2 trial,[11] gefitinib rapidly reduced symptoms in 35 percent to 43 percent of patients. In our trial, significantly more patients in the erlotinib group than in the placebo group had reductions in dyspnea, pain, and cough. Furthermore, the time to exacerbation of these symptoms was significantly longer in the erlotinib group. The analysis of the quality of life showed that symptom improvement was also associated with significantly improved physical function.

Rash[30] and diarrhea are the main toxic effects of EGFR inhibitors.[9] They led to dose reduction in 12 percent and 5 percent of patients, respectively, in our trial. Pneumonitis has been reported mainly in Japan following treatment with gefitinib.[31] However, four trials of gefitinib or erlotinib combined with chemotherapy for non–small-cell lung cancer reported similar rates of pneumonitis in active-treatment and placebo groups.[32-35] We rarely encountered pneumonitis or pulmonary fibrosis.

In summary, this trial shows that erlotinib, an oral tyrosine kinase inhibitor of EGFR, prolongs survival and decreases symptoms, as compared with placebo, in previously treated patients with non–small-cell lung cancer.

APPENDIX

The following investigators and centers participated in this National Cancer Institute of Canada Clinical Trials Group study: A.M. Alvarez, J.L. Martinez, M. Varela, M. Van Kooten, S. Jovtis, Buenos Aires; M. Freue, Lanus, Argentina; M. Rosenthal, Parkville, Australia; D. Yip, Garran, Australia; R. De Boer, Footscray, Australia; S. Ackland, Waratah, Australia; P. Clingan, Wollongong, Australia; D. Campos, San Isidro, Argentina; A. del Giglio, Santo Andre, Brazil; C. Mathias, Bahia, Brazil; I.L Santoro, J.R. Pereira, São Paulo; A.M. Murad, Belo Horizonte, Brazil; R.D.A. Ribeiro, Ceara, Brazil; S. Lago, Porto Alegre, Brazil; J. Vinholes, Porto Alegre, Brazil; R. Martins, Rio de Janeiro; S. Rorke, St. John's, Canada; W. Morzycki, Halifax, Canada; F. Laberge, R. Whittom, Ste.-Foy, Canada; V. Hirsh, J. Ayoub, Montreal; R.W. Gregg, Kingston, Canada; S. Laurie, Ottawa; F. Wierzbicki, Oshawa, Canada; B. Findlay, St. Catharines, Canada; A. Arnold, Hamilton, Canada; L.A. Zibdawi, Newmarket, Canada; J. Meharchand, F. Shepherd, R.L. Burkes, Y.C. Ung, Toronto; J.J. Wilson, Weston, Canada; B. Pressnail, Barrie, Canada; R. Myers, Mississauga, Canada; J. Noble, Sudbury, Canada; D. Walde, Sault Ste. Marie, Canada; S. Navaratnam, Winnipeg, Canada; H.I. Chalchal, Regina, Canada; D.G. Morris, Calgary, Canada; M. Smylie, Edmonton, Canada; D. Fenton, Kelowna, Canada; H. Martins, Victoria, Canada; J. Gutierrez, Las Condes, Chile; U. Gatzemeier, Grobhansdorf, Germany; J. von Pawel, Gauting, Germany; R. Loddenkemper, Berlin; A. Gerogianni, Athens; R. Chan, Pokfulam, Hong Kong; D. Flex, Petach Tikva, Israel; D. Loven, Afula, Israel; M.C. Wollner, Haifa, Israel; H. Biran, Rehovot, Israel; M. Levitt, Tel Hashomer, Israel; A. Cyjon, Zerifin, Israel; J. Lopez, Dviango, Mexico; J. Robles, Mexico City; G. Calderillo, Tlalpan, Mexico; T. Christmas, Auckland, New Zealand; A.B. Simpson, Wellington, New Zealand; M. Dediu, Bucharest, Romania; T.-E. Ciuleanu, Cluj-Napaca, Romania; M. Patran, Sibiu, Romania; L. Miron, Lasi, Romania; L. Ek, Lund, Sweden; B. Bergman, Gothenburg, Sweden; R. Soo, E.H. Tan, Singapore; S. Maoleekoonpairoj, A. Cheirsilpa, Bangkok, Thailand; S. Thongprasert, Chiangmai, Thailand; C.M. Rudin, Chicago; P. Ruff, Johannesburg, South Africa; D.J. Hacking, Westridge, South Africa; S.J. Fourie, Pretoria, South Africa; C. Jacobs, Port Elizabeth, South Africa; C.F. Slabber, Brooklyn Square, South Africa; D.A. Vorobiof, Parklands, South Africa; K. Chi-Hei, Pokfulam, Hong Kong; W. Arpornwirat, Bangkok, Thailand; M. Zukin, Rio de Janeiro.

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