Randomized Phase II Study of Gefitinib Compared With Placebo in Chemotherapy-Naïve Patients With Advanced Non–Small-Cell Lung Cancer and Poor Performance Status

Glenwood Goss, David Ferry, Rafal Wierzbicki, Scott A. Laurie, Joyce Thompson, Bonne Biesma, Fred R. Hirsch, Marileila Varella-Garcia, Emma Duffield, Ozlem U. Ataman, Marc Zarenda, and Alison A. Armour

From the Ottawa Hospital Cancer Center, Ottawa; AstraZeneca, Toronto; Durham Regional Cancer Center, Oshawa, Ontario, Canada; New Cross Hospital, Wolverhampton; Birmingham Heartlands Hospital, Birmingham; AstraZeneca, Macclesfield, United Kingdom; Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, the Netherlands; and the University of Colorado Cancer Center, Denver, CO.

Submitted June 9, 2008; accepted December 4, 2008; published online ahead of print at www.jco.org on March 16, 2009.

Supported by AstraZeneca.

Presented in part at the 12th World Conference on Lung Cancer, Seoul, Korea, September 2-6, 2007; the National Cancer Research Institute Annual Meeting, Birmingham, United Kingdom, September 30 to October 3, 2007; and at the 1st European Lung Cancer Conference, Geneva, Switzerland, April 23-26, 2008.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Glenwood Goss, MB, BCh, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, 501 Smyth Rd, Ottawa, Ontario K1H 8L6, Canada; e-mail: ggoss@ottawahospital.on.ca.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

© 2009 by American Society of Clinical Oncology

0732-183X/09/2713-2253/\$20.00

DOI: 10.1200/JCO.2008.18.4408

ABSTRACT

Purpose

To compare gefitinib with placebo in chemotherapy naïve patients with advanced non–small-cell lung cancer (NSCLC) and poor performance status.

Patients and Methods

NSCLC patients (chemotherapy naïve, WHO performance status 2 or 3; unfit for chemotherapy; stage IIIB/IV) were randomly assigned to gefitinib (250 mg/d) plus best supportive care (BSC; $n = 100$) or placebo plus BSC ($n = 101$). The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), objective response rate (ORR), quality of life (QOL), pulmonary symptom improvement (PSI), and safety. Correlation of gefitinib efficacy with *EGFR* gene copy number (fluorescent in situ hybridization [FISH]) was explored.

Results

Hazard ratios (HRs; gefitinib:placebo) were 0.82 (95% CI, 0.60 to 1.12; $P = .217$) for PFS and 0.84 (95% CI, 0.62 to 1.15; $P = .272$) for OS. As expected for this patient population, OS for both arms was poor, at about 3 months. ORRs were 6.0% (gefitinib) and 1.0% (placebo). QOL and PSI rates were 21.1% and 28.3% (gefitinib) and 20.0% and 28.3% (placebo), respectively. In *EGFR* FISH-positive patients ($n = 32$), HRs were 0.29 (95% CI, 0.11 to 0.73) for PFS and 0.44 (95% CI, 0.17 to 1.12) for OS. No unexpected adverse events occurred.

Conclusion

There was no statistically significant difference in PFS, OS, and ORRs after treatment with gefitinib or placebo, in the overall population; improvements in QOL and symptoms were similar in both groups. Tolerability profile of gefitinib was consistent with previous studies. PFS was statistically significantly improved for gefitinib-treated patients with *EGFR* FISH-positive tumors.

J Clin Oncol 27:2253-2260. © 2009 by American Society of Clinical Oncology

INTRODUCTION

An estimated 30% to 40% of patients with advanced non–small-cell lung cancer (NSCLC) have a poor performance status (PS).¹ PS is an independent prognostic factor for survival²; median survival for treated patients with a PS of 2 has been reported as between 2.9 to 5.8 months.²⁻⁶ For patients with metastatic NSCLC and good PS, platinum-based combination chemotherapy, with or without bevacizumab, is recommended as first-line treatment,⁷ based on the results of randomized controlled studies.⁸⁻¹¹ However, for patients with poor PS, there is less evidence to guide recommendations; such patients are usually underrepresented¹¹⁻¹⁴ or not enrolled in studies of first-line treatment for advanced disease. For PS 2 patients, single-agent

therapy is proposed as a reasonable alternative whereas first-line treatment options are limited to best supportive care (BSC) for PS 3 to 4 patients.⁷ In 2004, a panel of European experts agreed to the need for studies specifically dedicated to PS 2 NSCLC patients to provide further evidence to guide treatment decisions in this group.¹⁵

Gefitinib (IRESSA; AstraZeneca, Macclesfield, United Kingdom) is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). In two phase II monotherapy studies in advanced NSCLC patients who had received previous chemotherapy, gefitinib 250 mg/d was associated with an objective response rate (ORR) of 12% to 18%, symptom improvement, and a manageable tolerability profile.^{16,17} In the phase III IRESSA Survival Evaluation in Lung Cancer (ISEL) study of gefitinib

plus best supportive care (BSC) or placebo plus BSC, as second- or third-line treatment for refractory, advanced NSCLC, gefitinib was associated with some improvement in survival but this did not reach statistical significance in either the overall population or the subgroup of patients with adenocarcinoma.¹⁸ Recently, *EGFR* gene copy number measured by fluorescent in situ hybridization (FISH) has been suggested as a predictor for sensitivity to *EGFR*-TKIs.¹⁹⁻²²

The aim of the IRESSA NSCLC Trial Evaluating Poor Performance Status Patients (INSTEP) study was to assess whether the addition of gefitinib to BSC confers an improvement in terms of progression-free survival (PFS) in chemotherapy naïve patients with advanced NSCLC and poor PS. An exploratory end point was to investigate the correlation of gefitinib activity with *EGFR* gene copy number.

PATIENTS AND METHODS

Study Design

This phase II, randomized, double-blind, multicenter, parallel-group study compared gefitinib plus BSC with placebo plus BSC in chemotherapy naïve patients with advanced NSCLC and poor PS (INSTEP, D7913C00711, 1839IL/0711, NCT00259064). All patients provided written informed consent. The study was conducted in line with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

Patients were randomly assigned 1:1 according to a randomization scheme prepared by the biostatistics group, AstraZeneca, to receive either gefitinib (250 mg/d) plus BSC or placebo plus BSC. Gefitinib and placebo tablets were physically identical and presented in identical packaging. Patients were to receive gefitinib or placebo until clinical (in the opinion of the inves-

tigator; nonmeasurable lesion(s) or deterioration in health such that the patient could not complete objective assessment) or objective (radiological) progression (by Response Evaluation Criteria in Solid Tumors [RECIST]), unacceptable toxicity, or patient withdrawal. Patients with confirmed objective progression considered by the patient and investigator to be deriving clinical benefit could continue the blinded study treatment. Dose interruptions of up to 14 days were allowed to manage toxicity. All patients were observed for at least 2 months.

The primary end point of this study was PFS (date of random assignment to the earlier date of objective disease progression, assessed by RECIST,²³ or death due to any cause). Any patient who discontinued for reasons other than objective disease progression was to continue, where possible, to have objective tumor assessments every 6 weeks (including patients who subsequently started alternative anticancer therapies). Patients who had not progressed or died by the date of data cutoff were censored at their latest assessable objective tumor assessment, including patients lost to follow-up or who withdrew consent. Secondary end points were overall survival (OS; date of random assignment to date of death or last date known to be alive), ORR (RECIST),²³ quality of life (QOL), pulmonary symptom improvement (PSI), and safety.

QOL was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire,²⁴⁻²⁶ collected at 3-weekly intervals for 18 weeks, then 6-weekly, until 6 weeks postdisease progression. A diary card consisting of the Lung Cancer Subscale (LCS) of the FACT-L was also completed weekly. QOL improvements were defined as improvement from baseline in the FACT-L total score or trial outcome index (TOI; the physical well-being, functional well-being, and LCS domains of FACT-L) of at least 6 points²⁴ maintained for at least 21 days. LCS improvement was defined as an improvement of at least 2 points²⁴ maintained for at least 21 days. PSI was measured by the four pulmonary items of the seven-item LCS and, as validated for the LCS,^{24,27} defined as an improvement of at least 2 points maintained for at least 21 days in at least one pulmonary item of the LCS from a baseline score of moderate or severe.

Fig 1. Patient disposition.

Safety was assessed from the adverse event (AE) profile (type, frequency, and severity using National Cancer Institute Common Toxicity Criteria [CTC] version 3.0), laboratory parameters, and vital signs.

Correlation of gefitinib efficacy with *EGFR* gene copy number was a protocol-defined exploratory end point. *EGFR* gene copy number was measured by FISH in baseline tumor tissue samples.¹⁹

Patients

Patient eligibility included: age ≥ 18 years old, chemotherapy naïve, histologically or cytologically confirmed locally advanced or metastatic NSCLC not amenable to curative surgery or radiotherapy, WHO PS of 2 or 3, measurable disease (RECIST), no prior EGFR inhibitor therapy, and considered unfit for chemotherapy. Exclusion criteria detailed in the online-only Appendix.

Statistical Analysis

Sample size was calculated assuming a median PFS of 4 weeks for BSC; there were no data in this setting from which the effectiveness of gefitinib could be accurately anticipated. A total of 134 progression events were estimated to be sufficient to detect a 75% improvement in PFS with gefitinib with 90% power, or a 50% improvement with 81% power, assuming a two-sided α level of 5%. Two hundred randomly assigned patients observed for at least 2 months was estimated to be sufficient to observe these events. Patients were to be observed until 134 progression events had occurred and at least 200 patients had been observed for at least 2 months, whichever occurred last.

For the analyses of PFS and OS, a proportional hazards model was used to compare treatment groups with gender (male v female), WHO PS (2 v 3), histology (adenocarcinoma [including bronchoalveolar] v other), smoking history (ever v never), and stage (locally advanced v metastatic) as covariates. The hazard ratios (HRs; gefitinib:placebo) and associated 95% CIs and *P* values were estimated. ORR was compared between treatments using a logistic regression model, using the same covariates, and the odds ratio (OR) and associated 95% CI estimated. A HR lower than 1 and an OR higher than 1 indicate a favorable outcome for gefitinib compared with placebo. These analyses were performed on the intention-to-treat (ITT) population (all randomly assigned patients). Formal statistical analyses of subgroups defined by the covariates are not available because of the small subgroup sizes. QOL and PSI rates were analyzed using a logistic regression model with the same covariates and the OR and associated 95% CIs estimated. The assessable for QOL (patients with baseline and postbaseline QOL assessments) and assessable for PSI (patients with at least one LCS pulmonary item with a baseline score of 0 or 1 and a postbaseline assessment) populations were analyzed for QOL variables and PSI, respectively. Gefitinib:placebo HRs and 95% CIs were estimated for FISH-positive and FISH-negative subgroups for PFS and OS. PFS and OS comparisons between FISH subgroups were also performed for gefitinib and placebo separately. The assessable for safety population included all randomly assigned patients who received at least one dose of study treatment. Safety data were summarized but no formal statistical comparisons were made.

RESULTS

From September 2004 to December 2006, 201 patients were randomly assigned (Fig 1) from 37 centers in five countries (Australia [26], Canada [114], the Czech Republic [4], the Netherlands [17], and the United Kingdom [40]). Data cutoff was February 2007. The majority of patients were age ≥ 65 years, with nearly 50% of patients ≥ 75 years of age (Table 1). In the gefitinib group, 45% had a PS of 3 compared with 38% in the placebo group. In all, 45% of patients had adenocarcinoma (including bronchoalveolar carcinoma), 96% were white, 39% were female, and 9% were never-smokers.

At data cutoff, median exposure (including dose interruptions) was 50 days versus 46 days for gefitinib and placebo, respectively. Dose interruptions occurred in 27% versus 19% of gefitinib- and placebo-

Table 1. Baseline Patient Characteristics

Characteristic	Gefitinib (n = 100)		Placebo (n = 101)	
	No.	%	No.	%
Median age, years	74		76	
Range	43-89		42-90	
Age group, years				
< 45	1	1.0	1	1.0
45-64	18	18.0	16	15.8
65-74	35	35.0	32	31.7
≥ 75	46	46.0	52	51.5
Sex				
Male	61	61.0	61	60.4
Female	39	39.0	40	39.6
Ethnicity				
White	96	96.0	97	96.0
Asian	4	4.0	3	3.0
Other	0	0	1	1.0
Smoking history				
Ever	90	90.0	92	91.1
Never	10	10.0	9	8.9
WHO performance status				
2	55	55.0	63	62.4
3	45	45.0	38	37.6
Tumor histology				
Adenocarcinoma*	45	45.0	46	45.5
Squamous cell carcinoma	29	29.0	25	24.8
Large cell carcinoma	10	10.0	11	10.9
Undifferentiated	7	7.0	10	9.9
Not recorded	9	9.0	9	8.9
Disease stage at entry				
Locally advanced	16	16.0	17	16.8
Metastatic	84	84.0	84	83.2
Time from diagnosis to randomization, months				
< 6	67	67.0	69	68.3
6-12	12	12.0	13	12.9
> 12	21	21.0	19	18.8

*Includes six and 10 patients with bronchoalveolar carcinoma in the gefitinib and placebo groups, respectively.

treated patients, respectively. The median duration of interruption was 6 days versus 2 days and the majority of these patients, 22 of 27 and 17 of 19, had only one dose interruption with gefitinib and placebo, respectively. Based on an evaluation of dose received and dose planned, mean compliance was 96.8% for gefitinib (standard deviation, 7.8%) and 98.4% for placebo (standard deviation, 5.3%). Post-discontinuation, further systemic therapy was received by four patients in the gefitinib group (all chemotherapy) and six patients in the placebo group (one chemotherapy, five erlotinib).

Compliance rates for completion of the questionnaires over the course of the study were 63% versus 62% for FACT-L and 64% versus 62% for LCS for gefitinib versus placebo, respectively.

Efficacy

There was a trend toward improved PFS, OS, and ORR with gefitinib compared with placebo, although the differences did not reach statistical significance. The HRs for gefitinib compared with

placebo for PFS and OS were 0.82 (95% CI, 0.60 to 1.12; $P = .217$; Fig 2A) and 0.84 (95% CI, 0.62 to 1.15; $P = .272$; Fig 2B), respectively. Median OS was 3.7 months and 2.8 months for gefitinib and placebo, respectively. Median PFS values are uninformative in this setting because scans were performed at the standard 6-week interval and more than half of the patients progressed before their first scan. Hence, the median PFS values (43 days for gefitinib and 41 days for placebo) approximate to when the first scan took place at 6 weeks. The HR is a more accurate reflection of the treatment difference taking into account all of the information over the entire study period. Median durations of follow-up were 1.4 months and 1.3 months for PFS and 3.1 months and 2.7 months for OS for gefitinib and placebo, respectively. ORRs were 6.0% for gefitinib and 1.0% for placebo (OR, 6.57; 95% CI, 0.74 to 58.17); disease control (objective response plus stable disease) rates were 31.0% and 22.8%, respectively.

QOL improvement rates were 21.1% for gefitinib and 20.0% for placebo by FACT-L total score and 15.8% and 13.8%, respectively by FACT-L TOI (Fig 3). Symptom improvement rates were 32.9% and 30.8% for gefitinib and placebo, respectively for the FACT-L LCS, and 28.3% and 28.3%, respectively, for PSI (Fig 3).

Biomarker Analyses

Of the 201 patients randomly assigned, 100 patients provided a tumor sample for analysis and, of these, 84 were assessable as positive or negative for *EGFR* gene copy number by FISH. Demographic data for patients with known *EGFR* FISH status were generally comparable to the overall study population (data not shown). Mutation analysis was not performed due to the small number of patients with sufficient tissue sample to determine a mutation result.

In *EGFR* FISH-positive patients ($n = 32$), there was a significant improvement in PFS and numerically improved OS with gefitinib compared with placebo (HR, 0.29; 95% CI, 0.11 to 0.73; and HR, 0.44; 95% CI, 0.17 to 1.12, respectively; Fig 4). Whereas, in *EGFR* FISH-negative patients ($n = 52$), the HRs for PFS and OS were 0.74 (95% CI, 0.38 to 1.45) and 1.02 (95% CI, 0.56 to 1.88), respectively (Fig 4). In gefitinib-treated patients, the HR for PFS for FISH-positive ($n = 12$): FISH-negative patients ($n = 32$) was 0.26 (95% CI, 0.11 to 0.61); whereas, in placebo-treated patients, the HR for PFS for FISH-positive ($n = 20$): FISH-negative patients ($n = 20$) was 0.82 (95% CI, 0.41 to 1.62). The HRs for OS between the FISH-positive and FISH-negative

Fig 3. Improvement rates for quality of life (Functional Assessment of Cancer Therapy – Lung [FACT-L] total score and trial outcome index [TOI]) and symptom improvement (Lung Cancer Subscale [LCS] and pulmonary symptom improvement [PSI]). OR, odds ratio.

patients were 0.47 with gefitinib (95% CI, 0.21 to 1.05) and 0.95 with placebo (95% CI, 0.47 to 1.96).

Safety

All randomly assigned patients received at least one dose of study treatment and so were included in the assessable for safety population. The incidence of AEs, serious AEs, and AEs leading to death are summarized in Table 2 by relationship to treatment and by grade. Ten patients in the gefitinib group and three patients in the placebo group had an AE leading to death; none of these were considered related to treatment. The most commonly reported AEs for gefitinib were diarrhea (51.0%), rash (34.0%), nausea (30.0%), vomiting (21%), and anorexia (20%); these were mainly mild to moderate (Table 3) and many of these (eg, nausea, vomiting, and anorexia) were seen frequently across both treatment groups. There were no reports of interstitial lung disease-type events in patients treated with gefitinib but one was reported in a patient treated with placebo (CTCAE grade 2 pneumonitis).

Fig 2. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival. HR, hazard ratio.

Fig 4. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival by epidermal growth factor receptor (EGFR) fluorescent in situ hybridization (FISH) status (exploratory analyses). HR, hazard ratio.

DISCUSSION

We believe this was the first prospective randomized study in advanced NSCLC that specifically included PS 3 patients in the eligibility criteria. The results show that in unselected chemotherapy naïve patients with poor PS, no statistically significant improvement in PFS, OS, and ORR was observed after treatment with gefitinib or placebo. Improvements in QOL and symptoms were similar with gefitinib and placebo. In the exploratory analyses of the EGFR FISH-positive subgroup, gefitinib significantly improved PFS compared with placebo, and there was a trend in favor of gefitinib in terms of OS.

Patients in both treatment groups in this study appear to have progressed and died more quickly than in some other studies of gefitinib monotherapy in chemotherapy naïve patients,²⁸⁻³⁰ which may be attributable to the poor PS of the patient population in our study. In a phase II study of 72 chemotherapy naïve PS 2 to 3 advanced NSCLC patients, a median OS of 6.3 months with gefitinib was reported²⁹ compared with 3.7 months in our study; however, only 17% of patients had a PS of 3 compared with 45% of the gefitinib arm in our study. In a retrospective review of 52 patients with advanced NSCLC who had a worse PS (PS 3, 83%; PS 4, 17%; 40% were chemotherapy naïve) than in our study, the median OS with gefitinib was only 2.5 months.³¹ In the preplanned subgroup analysis of PS 2 to 3 patients in the ISEL study of second- or third-line treatment, survival data were

comparable with our study: median survival 2.9 months versus 2.5 months for gefitinib and placebo, respectively, and HRs for OS were similar (HR, 0.80; 95% CI, 0.65 to 0.99; $P = .039$ for ISEL; and HR, 0.82; 95% CI, 0.6 to 1.12; $P = .217$ for our study;¹⁸ AstraZeneca, data on file).

Posthoc exploratory analyses of our study revealed that PS 2 patients have better clinical outcomes than PS 3 patients, irrespective of treatment received. Also, whereas PS 2 patients had similar outcomes with gefitinib and placebo (PFS HR, 1.11; 95% CI, 0.73 to 1.69; OS HR, 1.06; 95% CI, 0.70 to 1.61), PS 3 patients appeared to have improved PFS (HR, 0.51; 95% CI, 0.31 to 0.82) and OS (HR, 0.64; 95% CI, 0.40 to 1.03) with gefitinib than placebo. As might be expected with relatively small sample sizes, there were some imbalances in the demographic characteristics between the subgroups (fewer adenocarcinoma patients in the PS 2 group than in the PS 3 group and more males than females in the PS 2 group). However, key characteristics (sex, histology, smoking history, and stage) were adjusted for in the analyses to try to account for any imbalances.

The tolerability profile of gefitinib in this study was consistent with that reported in previous monotherapy studies.¹⁶⁻¹⁸ The overall incidence of AEs was higher than generally reported in the literature for both gefitinib and placebo and may be attributable to the advanced age, comorbidity, and poor PS of the patient population.

The proportion of patients who were EGFR FISH-positive in this study (38%) is consistent with the ISEL (31%)²⁰ and IRESSA in

Table 2. Adverse Event Summary

AE	Gefitinib (n = 100)		Placebo (n = 101)	
	No.	%	No.	%
Any	93	93.0	94	93.1
Treatment-related	63	63.0	36	35.6
Any SAE	25	25.0	25	24.8
Treatment-related	4	4.0	1	1.0
Not leading to death	20	20.0	22	21.8
Treatment-related SAE not leading to death	4	4.0	1	1.0
Leading to death	10	10.0	3	3.0
Treatment-related SAE leading to death	0	0	0	0
Leading to discontinuation	14	14.0	7	6.9
Treatment-related AE leading to discontinuation	6	6.0	3	3.0
SAE leading to discontinuation	8	8.0	5	5.0
Treatment-related SAE leading to discontinuation	0	0	0	0
Any CTCAE grade 3 or 4	36	36.0	43	42.6
Treatment-related	9	9.0	4	4.0
Any CTCAE grade 3, 4, or 5 AE	41	41.0	46	45.5
Treatment-related	9	9.0	4	4.0

Abbreviations: AE, adverse event; SAE, serious adverse event; CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events.

NSCLC versus Vinorelbine Investigation in the Elderly (INVITE; 34%)²⁸ studies and with the study of Cappuzzo et al (32%).¹⁹ Unlike for FISH-positive patients, there was no strong evidence of a difference in efficacy between gefitinib and placebo for FISH-negative

patients, suggesting that a high *EGFR* gene copy number appears to be predictive of an enhanced gefitinib effect over placebo in chemotherapy naïve, poor PS patients. Although our study was based on a smaller number of samples and was in chemotherapy naïve rather than pretreated patients, these data are consistent with those shown for the ISEL study,²⁰ in which FISH-positive patients had a better survival with gefitinib compared with placebo (HR, 0.61; 95% CI, 0.36 to 1.04; $P = .067$) and FISH-negative patients showed no apparent difference (HR, 1.16; 95% CI, 0.81 to 1.64; $P = .417$; comparison of HRs FISH-positive ν FISH-negative, $P = .045$). Within the gefitinib group of our study, FISH-positive patients had better efficacy outcomes than FISH-negative patients, consistent with the gefitinib arm of ISEL²⁰ and several single-arm gefitinib studies.^{19,21} Furthermore, the HR for OS between the FISH-positive and FISH-negative patients for the placebo group was 0.95 (95% CI, 0.47 to 1.96), implying that FISH-positivity was not a prognostic factor in this study. However, these analyses should be interpreted with caution as they are nonrandomized comparisons and, with the exception of ISEL, patient numbers are small.

In conclusion, results from this study have shown that in unselected, chemotherapy naïve, predominantly Western patients with poor PS, there was no statistically significant improvement in PFS, OS, and ORR with gefitinib or with placebo, although the trend was in favor of gefitinib. In the *EGFR* FISH-positive subgroup, gefitinib significantly improved PFS compared with placebo and there was a trend in favor of gefitinib in terms of OS. This proof of principle randomized phase II study confirms that poor PS

Table 3. Adverse Events

Adverse Event	Gefitinib (n = 100)				Placebo (n = 101)			
	Any CTCAE Grade		CTCAE Grade 3, 4, 5*		Any CTCAE Grade		CTCAE Grades 3, 4, 5*	
	No.	%	No.	%	No.	%	No.	%
Nonhematologic								
Diarrhea	51	51.0	3	3.0	20	19.8	3	3.0
Rash	34	34.0	0	0	10	9.9	0	0
Nausea	30	30.0	0	0	33	32.7	4	4.0
Vomiting	21	21.0	0	0	14	13.9	0	0
Anorexia	20	20.0	2	2.0	17	16.8	0	0
Dry skin	19	19.0	0	0	1	1.0	0	0
Dyspnea	19	19.0	11	11.0	13	12.9	6	5.9
Constipation	17	17.0	1	1.0	19	18.8	1	1.0
Fatigue	15	15.0	6	6.0	22	21.8	8	7.9
Peripheral edema	13	13.0	1	1.0	13	12.9	2	2.0
Abdominal pain	11	11.0	1	1.0	9	8.9	2	2.0
Insomnia	11	11.0	0	0	4	4.0	0	0
Lower respiratory tract infection	11	11.0	0	0	8	7.9	4	4.0
Pruritus	9	9.0	0	0	2	2.0	0	0
Epistaxis	8	8.0	0	0	2	2.0	0	0
Dry eye	5	5.0	0	0	0	0	0	0
Hematologic								
Anemia	7	7.0	3	3.0	1	1.0	0	0

NOTE. Data are for adverse events with an incidence of $> 10\%$ in either group or differing by $\geq 5\%$ between groups in terms of any CTCAE grade.

Abbreviation: CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events.

*Ten patients in the gefitinib group and three patients in the placebo group had an adverse event leading to death; none of these were considered related to treatment.

patients (PS 2 or 3) with chemotherapy naïve advanced NSCLC can be studied prospectively.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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.

Employment or Leadership Position: Emma Duffield, AstraZeneca (U); Ozlem U. Ataman, AstraZeneca (C); Marc Zarenda, AstraZeneca (C); Alison A. Armour, AstraZeneca (C) **Consultant or Advisory Role:** Glenwood Goss, AstraZeneca (C); David Ferry, AstraZeneca (C); Scott A. Laurie, AstraZeneca (C); Fred R. Hirsch, AstraZeneca (C), Roche (C), Genentech (C), Merck (C), Pfizer (C), Boehringer Ingelheim (C), Lilly Oncology (C), Bristol Myers Squibb/Imclone (C), Ventana (C), Syndax (C) **Stock Ownership:** Emma Duffield, AstraZeneca; Ozlem U. Ataman, AstraZeneca; Alison A. Armour, AstraZeneca **Honoraria:** Glenwood Goss, AstraZeneca; David Ferry, AstraZeneca; Scott A. Laurie,

AstraZeneca; Fred R. Hirsch, AstraZeneca, Lilly Oncology **Research Funding:** David Ferry, AstraZeneca; Rafal Wierzbicki, AstraZeneca; Scott A. Laurie, AstraZeneca; Fred R. Hirsch, AstraZeneca, OSI, Genentech, Merck, Syndax, Genmab; Marileila Varella-Garcia, AstraZeneca **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Glenwood Goss, David Ferry, Fred R. Hirsch, Emma Duffield

Financial support: David Ferry

Provision of study materials or patients: Glenwood Goss, Rafal Wierzbicki, Scott A. Laurie, Joyce Thompson, Bonne Biesma

Collection and assembly of data: Glenwood Goss, Joyce Thompson, Fred R. Hirsch, Emma Duffield, Ozlem U. Ataman, Alison A. Armour

Data analysis and interpretation: David Ferry, Rafal Wierzbicki, Fred R. Hirsch, Marileila Varella-Garcia, Emma Duffield, Ozlem U. Ataman, Marc Zarenda, Alison A. Armour

Manuscript writing: Glenwood Goss, David Ferry, Rafal Wierzbicki, Scott A. Laurie, Joyce Thompson, Bonne Biesma, Emma Duffield, Ozlem U. Ataman, Marc Zarenda, Alison A. Armour

Final approval of manuscript: Glenwood Goss, David Ferry, Rafal Wierzbicki, Scott A. Laurie, Joyce Thompson, Bonne Biesma, Fred R. Hirsch, Marileila Varella-Garcia, Emma Duffield, Ozlem U. Ataman, Marc Zarenda, Alison A. Armour

REFERENCES

- Buccheri G, Ferrigno D, Tamburini M: Karnofsky and ECOG performance status scoring in lung cancer: A prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 32A:1135-1141, 1996
- Jiroutek M, Johnson D, Blum R, et al: Prognostic factors in advanced non-small cell lung cancer (NSCLC): Analysis of Eastern Cooperative Oncology Group (ECOG) trials from 1981-1992. *Proc Am Soc Clin Oncol* 18:461a, 1998 (abstr 1774)
- Jeremic B, Milicic B, Dagovic A, et al: Pre-treatment clinical prognostic factors in patients with stage IV non-small cell lung cancer (NSCLC) treated with chemotherapy. *J Cancer Res Clin Oncol* 129: 114-122, 2003
- Lilenbaum RC, Herndon JE, List MA, et al: Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: The cancer and leukemia group B (study 9730). *J Clin Oncol* 23:190-196, 2005
- Perrone F, Di Maio M, Gallo C, et al: Outcome of patients with a performance status of 2 in the Multicenter Italian Lung Cancer in the Elderly Study (MILES). *J Clin Oncol* 22:5018-5020, 2004
- Sweeney CJ, Zhu J, Sandler AB, et al: Outcome of patients with a performance status of 2 in Eastern Cooperative Oncology Group Study E1594: A phase III trial in patients with metastatic non-small cell lung carcinoma. *Cancer* 92:2639-2647, 2001
- National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology - v. 2.2008. Non-small cell lung cancer, 07 update. http://www.nccn.org/professionals/physician_gls/default.asp
- Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: A Southwest Oncology Group trial. *J Clin Oncol* 19: 3210-3218, 2001
- Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 311:899-909, 1995
- Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355:2542-2550, 2006
- Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 346:92-98, 2002
- Gridelli C, Perrone F, Gallo C, et al: Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 95:362-372, 2003
- Le Chevalier T, Brisgand D, Douillard J-Y, et al: Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multicenter trial including 612 patients. *J Clin Oncol* 12:360-367, 1994
- Scagliotti GV, De Marinis F, Rinaldi M, et al: Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 20:4285-4291, 2002
- Gridelli C, Ardizoni A, Le Chevalier T, et al: Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: Results of an European Experts Panel. *Ann Oncol* 15:419-426, 2004
- Fukuoka M, Yano S, Giaccone G, et al: Multinational randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 21:2237-2246, 2003
- Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. *JAMA* 290:2149-2158, 2003
- Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 366:1527-1537, 2005
- Cappuzzo F, Hirsch FR, Rossi E, et al: Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst* 97:643-655, 2005
- Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al: Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 24:5034-5042, 2006
- Hirsch FR, Varella-Garcia M, McCoy J, et al: Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: A Southwest Oncology Group study. *J Clin Oncol* 23:6838-6845, 2005
- Tsao M-S, Sakurada A, Cutz J-C, et al: Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med* 353:133-144, 2005
- Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 92:205-216, 2000
- Cella D, Eton DT, Fairclough DL, et al: What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol* 55:285-295, 2002
- Cella DF, Tully DS, Gray G, et al: The Functional Assessment of Cancer Therapy Scale: Development and validation of the general measure. *J Clin Oncol* 11:570-579, 1993
- Cella DF, Bonomi AE, Lloyd SR, et al: Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 12:199-220, 1995
- Cella D, Herbst RS, Lynch TJ, et al: Clinically meaningful improvement in symptoms and quality of life for patients with non-small-cell lung cancer

receiving gefitinib in a randomized controlled trial. *J Clin Oncol* 23:2946-2954, 2005

28. Crinò L, Zatloukal P, Reck M, et al: First-line gefitinib (IRESSA) versus vinorelbine (INVITE): A randomized phase II study in elderly patients with advanced non-small-cell lung cancer. *Ann Oncol* 18: iv11-iv15, 2007 (suppl 4; abstr 0.404)

29. Spigel DR, Hainsworth JD, Burkett ER, et al: Single-agent gefitinib in patients with untreated advanced non-small-cell lung cancer and poor performance status: A Minnie Pearl Cancer Res Network phase II trial. *Clin Lung Cancer* 7:127-132, 2005

30. Govindan R, Natale R, Wade J, et al: Efficacy and safety of gefitinib in chemo-naïve patients with

advanced non-small cell lung cancer treated in an expanded access program. *Lung Cancer* 53:331-337, 2006

31. Su WP, Yang CH, Yu CJ, et al: Gefitinib treatment for non-small cell lung cancer – a study including patients with poor performance status. *J Formos Med Assoc* 104:557-562, 2005

Acknowledgment

We thank Annette Smith, from Complete Medical Communications, who provided medical writing support.