VOLUME 30 · NUMBER 17 · JUNE 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Trial of Erlotinib Alone or With Carboplatin and Paclitaxel in Patients Who Were Never or Light Former Smokers With Advanced Lung Adenocarcinoma: CALGB 30406 Trial

Pasi A. Jänne, Xiaofei Wang, Mark A. Socinski, Jeffrey Crawford, Thomas E. Stinchcombe, Lin Gu, Marzia Capelletti, Martin J. Edelman, Miguel A. Villalona-Calero, Robert Kratzke, Everett E. Vokes, and Vincent A. Miller

See accompanying editorial on page 2025 and articles on pages 2046 and 2055

Pasi A. Jänne and Marzia Capelletti, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA; Xiaofei Wang, Jeffrey Crawford, and Lin Gu, Duke University Medical Center, Durham; Mark A. Socinski and Thomas E. Stinchcombe, University of North Carolina, Chapel Hill, NC; Martin J. Edelman, University of Maryland, Baltimore, MD; Miguel A. Villalona-Calero, The Ohio State University, Columbus, OH; Robert Kratzke, University of Minnesota, Minneapolis, MN; Everett E. Vokes, University of Chicago Medical Center, Chicago, IL; and Vincent A. Miller, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted October 18, 2011; accepted January 9, 2012; published online ahead of print at www.jco.org on April 30, 2012.

Written on behalf of Cancer and Leukemia Group B.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

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

Clinical Trials repository link available on JCO.org.

Corresponding author: Pasi A. Jänne, MD, PhD, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, 450 Brookline Ave, M422, Boston, MA 02115; e-mail: pjanne@partners.org.

0732-183X/12/3017-2063/$20.00

DOI: 10.1200/JCO.2011.40.1315

ABSTRACT

Purpose
Erlotinib is clinically effective in patients with non–small-cell lung cancer (NSCLC) who have adenocarcinoma, are never or limited former smokers, or have *EGFR* mutant tumors. We investigated the efficacy of erlotinib alone or in combination with chemotherapy in patients with these characteristics.

Patients and Methods
Patients with advanced NSCLC (adenocarcinoma) who were epidermal growth factor receptor tyrosine kinase inhibitor and chemotherapy naive never or light former smokers (smokers of > 100 cigarettes and ≤ 10 pack years and quit ≥ 1 year ago) were randomly assigned to continuous erlotinib or in combination with carboplatin and paclitaxel (ECP) for six cycles followed by erlotinib alone. The primary end point was progression-free survival (PFS). Tissue collection was mandatory.

Results
PFS was similar (5.0 *v* 6.6 months; $P = .1988$) in patients randomly assigned to erlotinib alone (arm A; n = 81) or to ECP (arm B; n = 100). *EGFR* mutation analysis was possible in 91% (164 of 181) of patients, and *EGFR* mutations were detected in 40% (51 of 128) of never smokers and in 42% (15 of 36) of light former smokers. In arm A, response rate (70% *v* 9%), PFS (14.1 *v* 2.6 months), and overall survival (OS; 31.3 *v* 18.1 month) favored *EGFR*-mutant patients. In arm B, response rate (73% *v* 30%), PFS (17.2 *v* 4.8 months), and OS (38.1 *v* 14.4 months) favored *EGFR*-mutant patients. Incidence of grades 3 to 4 hematologic (2% *v* 49%; $P < .001$) and nonhematologic (24% *v* 52%; $P < .001$) toxicity was greater in patients treated with ECP.

Conclusion
Erlotinib and erlotinib plus chemotherapy have similar efficacy in clinically selected populations of patients with advanced NSCLC. *EGFR* mutations identify patients most likely to benefit.

J Clin Oncol 30:2063-2069. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the leading cause of cancer mortality in the United States and in the world, and more than 85% of patients with lung cancer have non–small-cell lung cancer (NSCLC).[1] A majority of patients with lung cancer have stage IIIB or IV disease at the time of diagnosis, and palliative therapy with platinum-based double-agent chemotherapy is the standard therapy.[2] The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib is an effective treatment for patients with NSCLC for whom systemic chemotherapy has failed.[3] The efficacy of EGFR TKIs, including erlotinib, is greatest in the subset of patients with NSCLC who are never or limited former cigarette smokers.[3] This is likely because of the higher frequency of somatic mutations in the *EGFR* kinase domain in this phenotypic subset of patients with NSCLC.[4,5] This observation has been confirmed in prospective clinical trials.[6]

A phase III trial evaluated the role of adding erlotinib to first-line carboplatin and paclitaxel chemotherapy in patients with advanced NSCLC.[7] This strategy did not result in improvement in response rate (RR), time to progression, or overall

survival (OS) in the intent-to-treat patient population.[7] However, a subset analysis of patients who were never smokers revealed significant improvement in RR (30% *v* 11%; $P = .02$), time to progression (hazard ratio [HR], 0.50; 95% CI, 0.31 to 0.80; median, 6.0 and 4.3 months, respectively), and OS (HR, 0.49; 95% CI, 0.28 to 0.85; median, 22.5 and 10.1 months, respectively) for those treated in the erlotinib-containing arm compared with the chemotherapy and placebo arms.[7] One potential reason for this clinical observation is a combined benefit of chemotherapy and erlotinib in the subset of patients likely to benefit from erlotinib therapy. Alternatively, the outcome differences may have been solely the result of increased efficacy of erlotinib in never smokers and/or in patients with *EGFR*-mutant advanced NSCLC.[3] We thus developed a randomized phase II trial to investigate the efficacy of erlotinib alone and in combination with chemotherapy in patients selected based on clinical characteristics associated with known erlotinib benefit. At the time this trial was developed, routine *EGFR* mutation testing was not available. However, because of an interest in investigating the impact of *EGFR* mutations on the outcome of erlotinib-based therapy, tissue submission and specific tissue requirements were part of the trial eligibility.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have histologic documentation of primary lung adenocarcinoma; patients with bronchioloaveolar or adenosquamous carcinoma were eligible. Patients were required to have at least a core biopsy and be a never smoker (defined as smoking ≤ 100 cigarettes in lifetime) or former light smoker (defined as smoking > 100 cigarettes and ≤ 10 pack years and quit ≥ 1 year ago). Other eligibility criteria were stage IIIB disease with malignant pleural or pericardial effusion or stage IV disease, age ≥ 18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and measureable disease as defined by RECIST (Response Evaluation Criteria for Solid Tumors).[8] Laboratory requirements were an absolute neutrophil count ≥ 1,500/mL, platelet count ≥ 100,000/mL, hemoglobin ≥ 9.0 g/dL, renal function ≤ 1.5 mg/dL, total bilirubin less than upper limit of normal, and AST ≤ 2.5× upper limit of normal. No prior therapy with chemotherapy, erlotinib, or other agents targeting the EGFR pathway was allowed; radiation therapy and major surgery had to be completed ≥ 3 weeks before enrollment. Patients with brain metastases were required to be ≥ 3 weeks from completion of radiation therapy and asymptomatic and could not be receiving corticosteroid therapy. Patients with NSCLC not otherwise specified or those whose pathology consisted of only a fine needle aspirate were not eligible. This trial was approved by the institutional reviews boards of the participating institutions, and patients were required to provide informed consent before enrollment. This trial was registered with ClinicalTrials.gov.

Treatment

Patients were randomly assigned to erlotinib 150 mg daily alone (arm A) or erlotinib 150 mg daily continuous in combination with paclitaxel 200 mg/m^2 every 21 days and carboplatin area under the curve of 6 using the Calvert formula every 21 days (arm B) for up to six cycles; patients assigned to arm B continued to receive erlotinib after completion of chemotherapy.[9] Patients in both arms continued to receive erlotinib until disease progression or unacceptable toxicity. One cycle was defined as 21 days in both arms. Dose reductions for erlotinib were to 100 mg and 50 mg daily; one dose-level reduction was performed for grade 3 rash or diarrhea and grade ≥ 2 conjunctivitis. Erlotinib was discontinued for interstitial pneumonitis, grade 4 diarrhea or rash, and grade ≥ 2 keratitis. Patients in arm B were required to have an absolute neutrophil count ≥ 1,500/mL and platelets ≥ 100,000/mL on day 1 of each cycle; treatment could be delayed up to 2 weeks. Standard dose reductions were used for paclitaxel and carboplatin. Patients developing toxicity with paclitaxel and/or carboplatin had the option to continue one of the chemotherapy agents alone along with erlotinib or with erlotinib alone. Management of rash, diarrhea, supportive care, and antiemetics was at the discretion of the treating physician.

Trial Design and Statistical Considerations

The primary objective was to estimate progression-free survival (PFS) in each arm; secondary objectives included overall RR (ORR), OS, toxicity, and determination of PFS in patients with and without *EGFR* mutations in each arm. A total of 180 eligible patients (arm A, 80; arm B, 100) were to be accrued. Sample size was determined to have adequate power to address the primary objective. For arm A, it was prespecified that if median PFS were ≤ 2.9 months, it would not be of further interest; if median PFS were ≥ 4.3 months, it would be worthy of further investigation. Assuming constant hazards, it was equivalent to test H_0: 18-week PFS ≤ 37% *v* H_1: 18-week PFS ≥ 52% for arm A. For arm B, it was determined that if treatment were associated with median PFS ≤ 4.0 months, it would not be of further interest; if median PFS were ≥ 6.0 months, the regimen would be worthy of further investigation. Assuming constant hazards, it was equivalent to test H_0: 18-week PFS ≤ 49% *v* H_1: 18-week PFS ≥ 62% for arm B. The size of arms A and B allowed the testing of each hypothesis at a one-sided significance level of .10 with approximately 90% power. This trial was not designed to have adequate power to compare the efficacy of the two arms.

The expected frequency of *EGFR* mutations in this patient population was 15%. It was assumed that the RRs for *EGFR*–wild-type and -mutant patients were 10% and 60% in arm A, respectively. With 80 patients in arm A, there was 96% power to detect a 50% increase in RR between *EGFR*–wild-type and -mutant patients, at a significance level of .05 with a two-sided χ^2 test. With 76 events, the study had 95% power, at a significance level of .05 using a two-sided log-rank test, to detect an HR of 0.31 (3 *v* 9.5 months) for PFS in favor of *EGFR*-mutant patients. In arm B, it was assumed that the RRs were 25% and 75% for *EGFR*–wild-type and -mutant patients, respectively. With 100 patients, there was 97% power to detect a 50% increase in RR between *EGFR*–wild-type and -mutant patients, at a significance level of .05 with a two-sided χ^2 test. With 89 events, the study had 83% power, at a significance level of .05 using a two-sided log-rank test, to detect an HR of 0.42 (5 *v* 12 months) for PFS in favor of *EGFR*-mutant patients.

PFS was defined as the time between random assignment and disease progression or death (whichever occurred first); OS was defined as the time from random assignment until death resulting from any cause. Kaplan-Meier product limit estimator was used to estimate median PFS and OS as well as 95% CIs.[10] The proportion of patients who experienced a response (partial or complete) and the exact 95% CI were estimated. Rates of treatment-related adverse events by type between arms were compared by Fisher's exact test. All *P* values are two sided.

EGFR Mutation Analysis

EGFR mutations were performed at the Dana-Farber Cancer Institute (Boston, MA) using a sensitive heteroduplex method coupled with enzymatic digestion as previously described.[11] All positive findings were independently verified and subjected to sequencing. The mutation analyses were blinded to the patients' clinical outcome.

On-Study Assessment

Patients were required to undergo history and physical examination, tumor measurements, complete blood count, and serum chemistries at baseline. Patients underwent computed tomography of the chest and abdomen including the liver and adrenals, bone scan, and computed tomography or magnetic resonance imaging of the brain before registration. Patients underwent reimaging every two cycles (6 weeks) until disease progression or unacceptable toxicity. Patients were evaluated every cycle (3 weeks) via history and physical examination, complete blood count, and serum chemistries, and toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

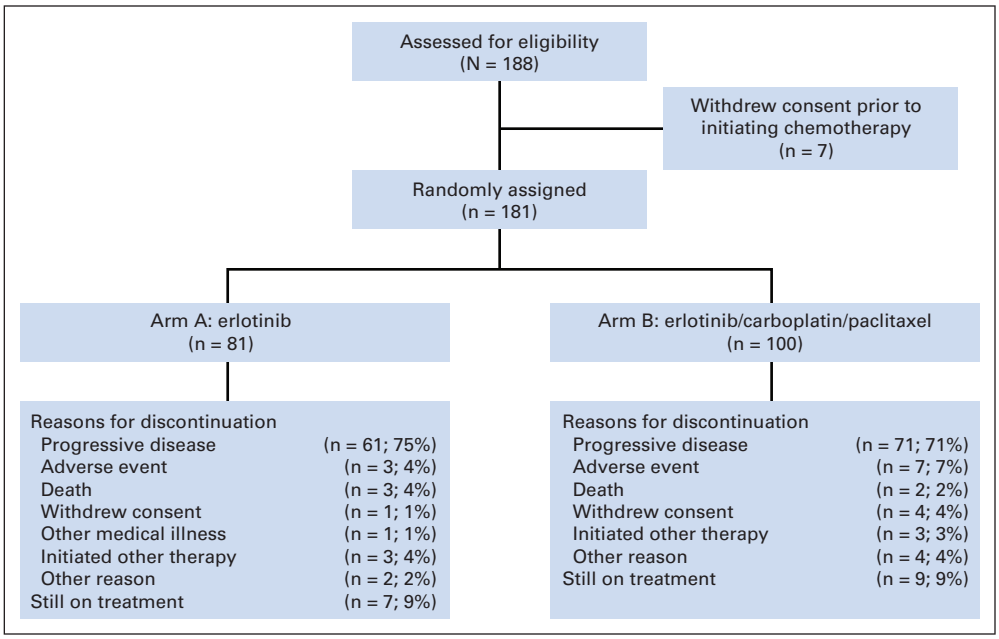

Fig 1. CONSORT diagram showing patient disposition.

RESULTS

Patient Characteristics and Treatment Administration

Between August 2005 and April 2009, 188 patients were enrolled; seven patients withdrew consent before initiating study therapy; 81 patients in arm A and 100 in arm B received study therapy (Fig 1). A majority of the patients were female (59%), were white (80%), had a performance score of 0 (54%), were never smokers (79%), and had adenocarcinoma histology (86%; Table 1). The median number of cycles of erlotinib in arm A was six (range, one to 70). The median number of cycles of therapy in arm B was eight (range, one to 70); the median number of cycles of the combination of erlotinib, carboplatin, and paclitaxel was three (range, one to six). Twenty-seven percent (48 of 181) of patients (arm A, 28%; arm B, 25%) received ≥ 18 cycles (1 year) of therapy.

Toxicity

In arm A, 23% of patients had a dose reduction in at least one cycle. In arm B, 27% of patients had a dose reduction in at least one cycle. The most common reason for treatment discontinuation in both arms was progressive disease: 61 patients (75%) in arm A and 71 patients (71%) in arm B. The rates of grades 3 to 4 hematologic toxicity were significantly higher (49% *v* 2%; $P < .001$) in arm B compared with arm A (Table 2). Similarly, the rates of nonhematologic toxicity (52% *v* 24%; $P < .001$) were greater in arm B compared with arm A. The rate of grade 3 acne/acneiform rash was similar in arms A and B (Table 2). Two patients in arm B experienced treatment-related death, one patient as a result of renal failure and one as a result of an adverse event not associated with a CTCAE term.

Efficacy

Median follow-up for all patients was 38 months, and all 181 patients were evaluable for PFS and OS. In the treated patient population, the ORR in arm A was 35% (95% CI, 24 to 46; n = 28), and 28 patients (35%) experienced stable disease; median PFS and OS were 5.0 (95% CI, 2.9 to 7.0) and 24.6 months (95% CI, 18.4 to 33.8), respectively (Fig 2A). In arm B, the ORR was 46% (95% CI, 36 to 56; n = 46), and 38 patients (38%) experienced stable disease; median PFS

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Erlotinib		Erlotinib Plus Carboplatin and Paclitaxel		All Patients	
	No.	%	No.	%	No.	%
No. of patients	81		100		181	
Age, years						
Median	58		60		59	
Range	32-78		34-81		32-81	
Sex						
Male	32	40	42	42	74	41
Female	49	60	58	58	107	59
Ethnicity						
White	61	75	84	84	145	80
African American	12	15	6	6	18	10
Asian	5	6	8	8	13	7
Other	2	3	1	1	3	2
Unknown	1	1	1	1	2	1
ECOG performance status						
0	50	62	48	48	98	54
1	31	38	52	52	83	46
Smoking history						
Never smoker	64	79	79	79	143	79
Light former smoker	17	21	21	21	38	21
Histology						
Adenocarcinoma	71	88	84	84	155	86
Bronhioloalveolar cancer	2	2	2	2	4	2
Adenocarcinoma with bronchioloalveolar features	8	10	14	14	22	12

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Common Adverse Events

Adverse Event	Erlotinib Grade 3 No.	Erlotinib Grade 3 %	Erlotinib Grade 4 No.	Erlotinib Grade 4 %	Erlotinib Plus Carboplatin and Paclitaxel Grade 3 No.	Erlotinib Plus Carboplatin and Paclitaxel Grade 3 %	Erlotinib Plus Carboplatin and Paclitaxel Grade 4 No.	Erlotinib Plus Carboplatin and Paclitaxel Grade 4 %	P*
Hematologic									
Anemia	1	1	0	0	7	7	0	0	.0763
Febrile neutropenia	0	0	0	0	9	9	3	3	< .001
Neutropenia	0	0	0	0	24	24	17	17	< .001
Thrombocytopenia	0	0	0	0	1	1	4	4	.0659
Maximum	2	2	0	0	29	29	20	20	< .001
Nonhematologic									
Allergic reaction (hypersensitivity)	0	0	0	0	4	4	0	0	.1291
Diarrhea	4	5	0	0	7	7	0	0	.7567
Fatigue	1	1	0	0	16	16	1	1	< .001
Nausea	1	1	0	0	7	7	0	0	.0763
Neuropathy (sensory)	0	0	0	0	6	6	0	0	.0338
Rash (acne/acneiform)	6	7	0	0	10	10	0	0	.6068
Vomiting	1	1	0	0	7	7	0	0	.0763
Maximum	18	22	2	2	39	39	13	13	< .001

NOTE. Comparisons are for grades 3 to 4 toxicities between erlotinib and erlotinib plus chemotherapy.
*Fisher's exact test.

and OS were 6.6 (95% CI, 5.4 to 8.2) and OS 19.8 months (95% CI, 14.4 to 27.8), respectively (Fig 2B). The primary end point was met in both arms of the study. The 18-week PFS rate for arm A was 52% (80% CI, 45 to 59); the lower limit of the 80% CI is above the prespecified limit of no interest in H_0 (< 37%). Similarly, the 18-week PFS rate for arm B was 69% (80% CI, 62 to 74), and the lower limit of the 80% CI is above the prespecified limit of no interest in H_0 (< 49%).

Efficacy in EGFR*-Mutant and Wild-Type Patients*

EGFR mutation analysis was successfully performed in 164 patients (91%); 17 patients had insufficient material or DNA for analysis (demographics listed in Appendix Table A1, online only). The mutational analysis was successfully performed in 77 (95%) of 81 patients in arm A and 87 (87%) of 100 patients in arm B. *EGFR*-activating drug-sensitive mutations, deletions of exon 19, and L858R point mutations were detected in 33 patients (43%) in arm A and 33 patients (38%) in arm B. In arm A, exons 19 and 21 mutations were detected in 23 and 10 tumor respectively; in Arm B exon 19 and 21 mutations were detected in 16 and 17 tumors, respectively. Six patients had *EGFR* exon 20 insertion mutations associated with erlotinib resistance (Appendix Table A2, online only).[12] The outcome analyses were limited to patients with exon 19 deletions and L858R mutations to compare findings from the current study with those of prospective clinical trials limited to exons 19 and 21 *EGFR*-mutant patients with NSCLC.[13-15] The frequency of *EGFR* mutations in never smokers (40%; 51 of 128) was similar ($P = .84$) to the frequency in former light smokers (42%; 15 of 36), consistent with prior observations.[16] In both arms, the ORR was significantly greater ($P < .001$) for patients with *EGFR*-mutant tumors (Table 3). Similarly, median PFS and OS were significantly longer for patients with *EGFR*-mutant tumors compared with those with *EGFR*–wild-type tumors in both arms of the study (Table 3; Figs 3A to 3D). PFS and OS for *EGFR*-mutant patients were similar in both arms of the study (Table 3; Appendix Fig A1, online only).

We also analyzed the outcome of patients based on the specific *EGFR* mutation (exon 19 deletion *v* L858R). Patients with *EGFR* exon 19 deletion mutations had a significantly greater RR to erlotinib (83% *v* 40%; $P = .0349$) compared with those with L858R mutations (Appendix Table A3, online only). PFS was numerically longer for patients with *EGFR* exon 19 mutations treated in either arm A or B compared with those with L858R mutations (Appendix Table A3). OS was similar for patients with *EGFR* exon 19 deletions and L858R tumors (Appendix Table A3).

DISCUSSION

Patients with NSCLC whose tumors harbor *EGFR* mutations derive the greatest degree of benefit from first-line EGFR TKI therapy.[6] These observations have been validated in retrospective and prospective clinical trials, and currently EGFR TKIs are commonly used as first-line therapy for advanced *EGFR*-mutant NSCLC.[6,13,15,17] Our findings are consistent with prior observations. The outcome (RR and

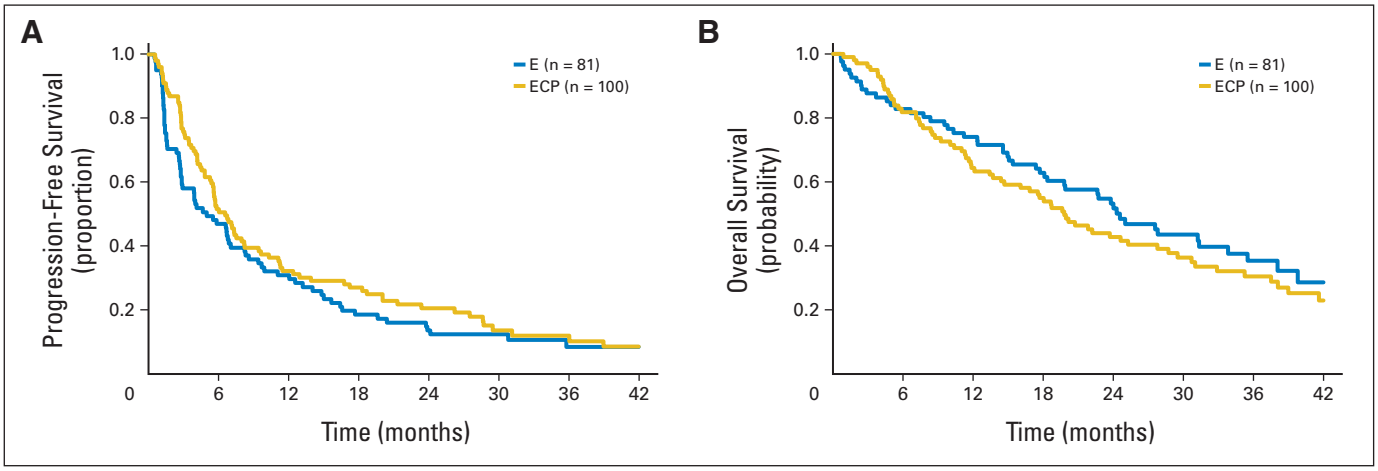

Fig 2. (A) Progression-free survival and (B) overall survival in all patients. E; erlotinib, ECP; erlotinib plus carboplatin and paclitaxel.

Table 3. Efficacy Analysis by *EGFR* Mutation Status

Outcome	Erlotinib			Erlotinib Plus Carboplatin and Paclitaxel		
	EGFR Mutant	*EGFR* WT	*P**	*EGFR* Mutant	*EGFR* WT	*P**
No. of patients	33	44		33	54	
ORR, %	70	9	< .001†	73	30	< .001†
95% CI	51 to 84	3 to 22		18 to 44	18 to 44	
PFS, months			< .001‡			< .001‡
Median	14.1	2.6		17.2	4.8	
95% CI	7.0 to 19.6	1.4 to 3.9		8.2 to 28.7	2.8 to 5.6	
OS, months			.0198‡			.0011‡
Median	31.3	18.1		38.1	14.4	
95% CI	23.8 to NA	9.5 to 27.8		19.6 to NA	8.7 to 20.2	

Abbreviations: NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; WT, wild type.
*Mutant *v* WT.
†Fisher's exact test.
‡Two-sided log-rank test.

PFS) of patients with *EGFR* mutations treated with erlotinib alone (arm A) was similar to that in other prospective studies, in both white and Asian patients, of erlotinib in treatment-naive *EGFR*-mutant patients.[15,18] The poor PFS in the *EGFR*–wild-type patients treated with erlotinib alone was also similar to that in prior studies of EGFR inhibitors in *EGFR*–wild-type patients or in those clinically unlikely to harbor an *EGFR* mutation.[6,19] The current study further reinforces the importance of molecular rather than phenotypic selection of patients for first-line EGFR TKI therapy.[6,18] This is particularly important for white patients, in whom, even in this highly clinically enriched patient

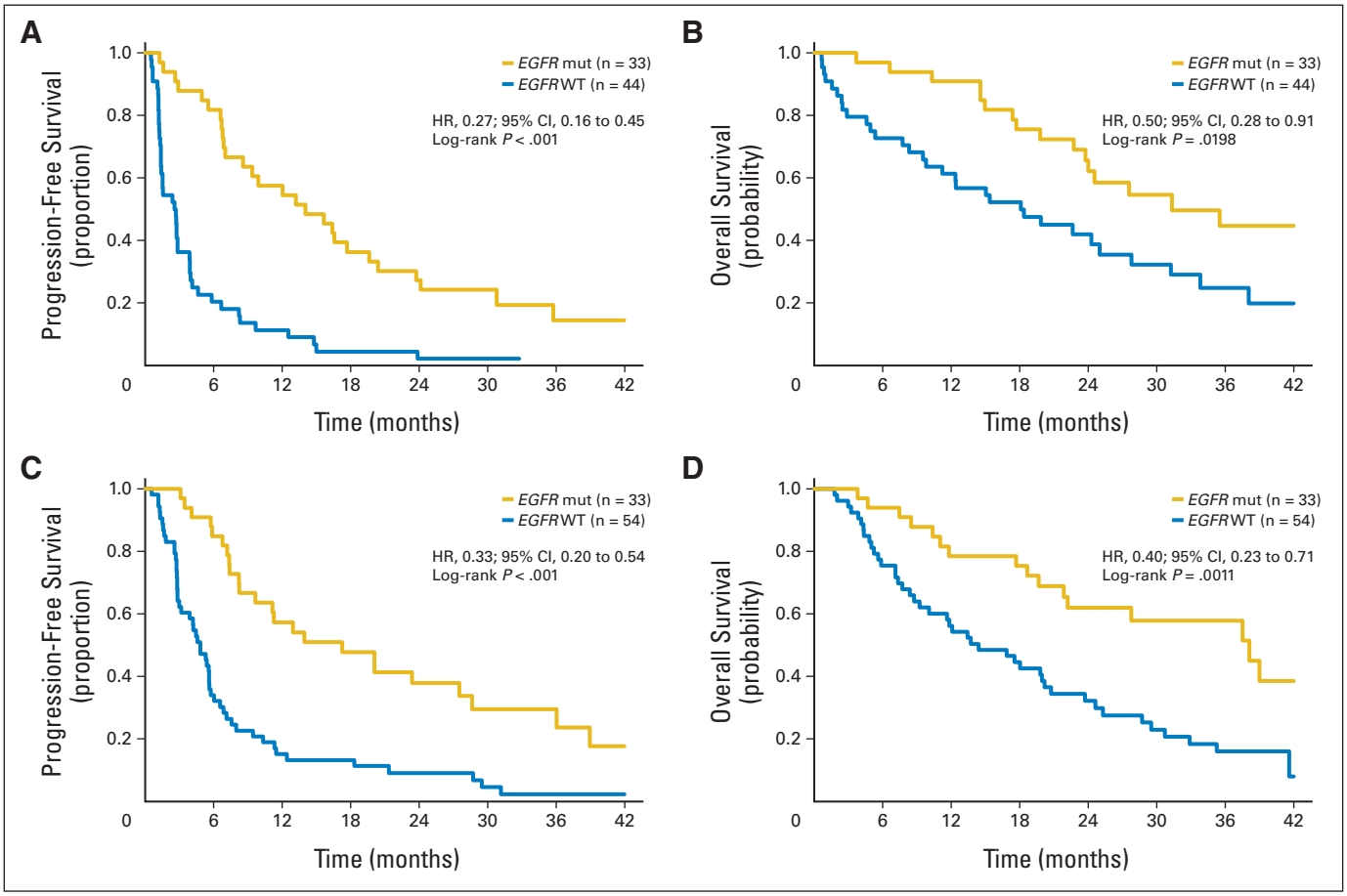

Fig 3. (A) Progression-free (PFS) and (B) overall survival (OS) based on *EGFR* mutation (mut) in arm A (erlotinib alone). (C) PFS and (D) OS based on *EGFR* mut in arm B (erlotinib plus carboplatin and paclitaxel). HR, hazard ratio; WT, wild type.

population, the frequency of *EGFR* mutations was only 40% compared with 60% in Asian patients with similar phenotypes.[6] Clinical trials have demonstrated that in unselected white patients who are unlikely to have *EGFR*-mutant tumors, first-line erlotinib therapy is associated with a survival detriment when compared with platinum-based chemotherapy.[19,20]

An important unresolved issue that in part led to the design of this trial was whether in the population of patients most sensitive to erlotinib (ie, *EGFR*-mutant patients) there would be any additional clinical benefit with the addition of systemic chemotherapy. Our findings would suggest that there is little, if any, such benefit (as measured by RR and PFS) in combining chemotherapy with erlotinib compared with erlotinib alone in *EGFR*-mutant patients (Table 3; Appendix Fig A1, online only). However, these findings should not be considered definitive, because the two-arm phase II trial was not designed to make formal comparison of these end points between the regimens. Our study, using continuous erlotinib therapy, also does not support the notion that EGFR TKIs and chemotherapy are antagonistic with one another.[21] In fact, even among *EGFR*–wild-type patients, in both arms, OS was longer than OS observed in recent phase III trials.[22,23] A randomized phase II trial conducted in Asia using intermittent erlotinib with chemotherapy demonstrated significantly longer PFS compared with chemotherapy alone.[24] However, this study did not include an erlotinib-only arm or detailed molecular analyses on the majority of patients to determine whether a similar outcome would have been observed with single-agent erlotinib therapy.[24] Intriguingly, the findings from *EGFR*-mutant NSCLC are in contrast with those in *HER2*-amplified breast cancer, in which, although trastuzumab has single-agent activity, the majority of the clinical benefit is derived from the combination of trastuzumab with chemotherapy.[25,26]

Improving PFS of patients with *EGFR*-mutant NSCLC treated with erlotinib remains a critical therapeutic challenge. Our study suggests that this is unlikely to be achieved by adding chemotherapy to erlotinib. Current studies are evaluating the benefit of the addition of bevacizumab to erlotinib in *EGFR*-mutant NSCLC based on a subset analysis of a prior clinical trial.[27] Additional efforts aimed at understanding the biology of *EGFR*-mutant NSCLC and/or the development of more effective EGFR-targeted therapies are necessary to improve the outcome of patients with *EGFR*-mutant NSCLC.[28,29]

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: None **Consultant or Advisory Role:** Pasi A. Jänne, Boehringer Ingelheim (C), Pfizer (U), AstraZeneca (C), Roche (C), Genentech (C); Thomas E. Stinchcombe, Genentech (C), Eli Lilly (C); Martin J. Edelman, Genentech (C), OSI Pharmaceuticals (C); Vincent A. Miller, Astellas Pharma (C), Boehringer Ingelheim (C), Clovis Oncology (C), Genentech (C) **Stock Ownership:** None **Honoraria:** Mark A. Socinski, Genentech; Jeffrey Crawford, Genentech; Vincent A. Miller, Astellas Pharma, Boehringer Ingelheim, Clovis Oncology, Genentech **Research Funding:** Mark A. Socinski, Genentech; Thomas E. Stinchcombe, Genentech, Pfizer, GlaxoSmithKline, Synta Pharmaceuticals; Miguel A. Villalona-Calero, Genentech; Vincent A. Miller, Boehringer Ingelheim, Genentech, ImClone Systems, Novartis, Pfizer **Expert Testimony:** None **Other Remuneration:** Pasi A. Jänne, Genzyme

AUTHOR CONTRIBUTIONS

Conception and design: Pasi A. Jänne, Xiaofei Wang, Mark A. Socinski, Robert Kratzke, Everett E. Vokes, Vincent A. Miller
Administrative support: Thomas E. Stinchcombe, Everett E. Vokes
Provision of study materials or patients: Pasi A. Jänne, Xiaofei Wang, Mark A. Socinski, Jeffrey Crawford, Thomas E. Stinchcombe, Marzia Capelletti, Martin J. Edelman, Miguel A. Villalona-Calero, Robert Kratzke, Everett E. Vokes, Vincent A. Miller
Collection and assembly of data: Xiaofei Wang, Mark A. Socinski, Jeffrey Crawford, Thomas E. Stinchcombe, Miguel A. Villalona-Calero, Robert Kratzke, Everett E. Vokes
Data analysis and interpretation: Pasi A. Jänne, Xiaofei Wang, Mark A. Socinski, Thomas E. Stinchcombe, Lin Gu, Marzia Capelletti, Martin J. Edelman, Vincent A. Miller
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300, 2010
2. 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
3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005
4. Paez JG, Jänne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004
5. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101:13306-13311, 2004
6. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009
7. Herbst RS, Prager D, Hermann R, et al: TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non–small-cell lung cancer. J Clin Oncol 23:5892-5899, 2005
8. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
9. Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989
10. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
11. Janne PA, Borras AM, Kuang Y, et al: A rapid and sensitive enzymatic method for epidermal growth factor receptor mutation screening. Clin Cancer Res 12:751-758, 2006
12. Wu JY, Wu SG, Yang CH, et al: Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response. Clin Cancer Res 14:4877-4882, 2008
13. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010
14. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010
15. Rosell R, Moran T, Queralt C, et al: Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 361:958-967, 2009

16. Shigematsu H, Lin L, Takahashi T, et al: Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97:339-346, 2005

17. Jackman DM, Miller VA, Cioffredi LA, et al: Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: Results of an online tumor registry of clinical trials. Clin Cancer Res 15:5267-5273, 2009

18. Zhou C, Wu YL, Chen G, et al: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735-742, 2011

19. Gridelli C, Ciardiello F, Feld R, et al: International multicenter randomized phase III study of first-line erlotinib (E) followed by second-line cisplatin plus gemcitabine (CG) versus first-line CG followed by second-line E in advanced non-small cell lung cancer (aNSCLC): The TORCH trial. J Clin Oncol 28:540s, 2010 (suppl; abstr 7508)

20. Lilenbaum R, Axelrod R, Thomas S, et al: Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. J Clin Oncol 26:863-869, 2008

21. Davies AM, Ho C, Lara PN Jr, et al: Pharmacodynamic separation of epidermal growth factor receptor tyrosine kinase inhibitors and chemotherapy in non-small-cell lung cancer. Clin Lung Cancer 7:385-388, 2006

22. 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

23. Reck M, von Pawel J, Zatloukal P, et al: Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: Results from a randomised phase III trial (AVAiL). Ann Oncol 21: 1804-1809, 2010

24. Mok TS, Wu YL, Yu CJ, et al: Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non–small-cell lung cancer. J Clin Oncol 27:5080-5087, 2009

25. Vogel CL, Cobleigh MA, Tripathy D, et al: Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20:719-726, 2002

26. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001

27. Herbst RS, Ansari R, Bustin F, et al: Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial. Lancet 377: 1846-1854, 2011

28. Bivona TG, Hieronymus H, Parker J, et al: FAS and NF-kappaB signalling modulate dependence of lung cancers on mutant EGFR. Nature 471:523-526, 2011

29. Zhou W, Ercan D, Chen L, et al: Novel mutant-selective EGFR kinase inhibitors against EGFR T790M. Nature 462:1070-1074, 2009