

A Randomized, Phase II, Biomarker-Selected Study Comparing Erlotinib to Erlotinib Intercalated With Chemotherapy in First-Line Therapy for Advanced Non–Small-Cell Lung Cancer

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A B S T R A C T

Purpose

Erlotinib prolongs survival in patients with advanced non–small-cell lung cancer (NSCLC). We report the results of a randomized, phase II study of erlotinib alone or intercalated with chemotherapy (CT + erlotinib) in chemotherapy-naïve patients with advanced NSCLC who were positive for epidermal growth factor receptor (EGFR) protein expression and/or with high *EGFR* gene copy number.

Patients and Methods

A total of 143 patients were randomly assigned to either erlotinib 150 mg daily orally until disease progression (PD) occurred or to chemotherapy with paclitaxel 200 mg/m² intravenously (IV) and carboplatin dosed by creatinine clearance (AUC 6) IV on day 1 intercalated with erlotinib 150 mg orally on days 2 through 15 every 3 weeks for four cycles followed by erlotinib 150 mg orally until PD occurred (CT + erlotinib). The primary end point was 6-month progression-free survival (PFS); secondary end points included response rate, PFS, and survival. *EGFR*, *KRAS* mutation, EGFR fluorescent in situ hybridization and immunohistochemistry, and E-cadherin and vimentin protein levels were also assessed.

Results

Six-month PFS rates were 26% and 31% for the two arms (CT + erlotinib and erlotinib alone, respectively). Both were less than the historical control of 45% ($P = .001$ and $P = .011$, respectively). Median PFS times were 4.57 and 2.69 months, respectively. Patients with tumors harboring *EGFR* activating mutations fared better on erlotinib alone (median PFS, 18.2 months v 4.9 months for CT + erlotinib).

Conclusion

The feasibility of a multicenter biomarker-driven study was demonstrated, but neither treatment arms exceeded historical controls. This study does not support combined chemotherapy and erlotinib in first-line treatment of EGFR-selected advanced NSCLC, and the patients with tumors harboring *EGFR* mutations had a better outcome on erlotinib alone.

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INTRODUCTION

Erlotinib, an epidermal growth factor receptor (EGFR) –directed tyrosine kinase inhibitor (TKI), prolongs progression-free survival (PFS) and overall survival (OS) in unselected patients with non–small-cell lung cancer (NSCLC) in the first-line, second/third-line and first-line maintenance therapies.^{1–3} Randomized studies of chemotherapy in combination with erlotinib demonstrated no advantage and possible antagonism among these therapies in an unselected population.^{4,5} Preclinical studies suggested that G1 cell cycle arrest induced by

erlotinib could interfere with the G2/M cytotoxicity of taxanes and suggested that appropriate scheduling of erlotinib with taxanes produce additive or synergistic growth inhibition.⁶ We previously demonstrated that patients with advanced NSCLC who were negative for *EGFR* by both fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) had no benefit from gefitinib therapy in the second/third-line setting.⁷

These studies led to the current randomized, phase II study evaluating erlotinib versus chemotherapy intercalated with erlotinib in chemotherapy-naïve patients with advanced NSCLC who were

positive for EGFR protein expression and/or high *EGFR* gene copy number. This study was initiated before the results from the Iressa Pan-Asia Study (IPASS), which identified the significance of *EGFR* mutation testing before first-line therapy, was available.⁸ Other goals were to determine the feasibility of a prospective biomarker multicenter study and to select a treatment arm for a randomized, phase III trial.

PATIENTS AND METHODS

Study Design

This was an international, randomized, phase II study of erlotinib as single-agent treatment or of carboplatin/paclitaxel chemotherapy intercalated with erlotinib in newly diagnosed patient with NSCLC who had EGFR-positive tumors assessed by IHC or FISH. Thirty-seven centers in the United States and five in the United Kingdom participated. The primary end point was the percentage of patients alive and without tumor progression at 6 months (ie, 6-month PFS). Secondary end points included tumor response rate (RR), PFS, and OS as well as the exploration of the correlation between clinical outcome and biomarkers of interest. Key inclusion criteria were sufficient tumor tissue sample for EGFR testing; histologically or cytologically advanced (ie, stages IIIB or IV) NSCLC; radiologically measurable or evaluable disease; and adequate organ function. Patients who received any prior or concurrent anticancer therapy for advanced NSCLC and patients who had uncontrolled brain metastases were excluded.

Web-based, centralized random assignment was performed by IDDI (Brussels, Belgium) by using an adaptive random assignment method by Pocock and Simon.⁹ Patients were stratified by the number of positive tests for EGFR expression (by IHC, FISH: 1 or 2) smoking status (current, former, or never), ECOG performance status (0/1 or 2), and extent of disease (stage IIIB or IV).

The study was approved by each institution's institutional review board/ethics committee. Written informed consent was obtained from all patients for participation, including for tissue analyses and banking.

Treatment

Patients were randomly assigned (1:1) to receive erlotinib 150 mg orally until disease progression (PD) occurred or to receive chemotherapy (paclitaxel 200 mg/m² intravenously [IV] and carboplatin dosed by creatinine clearance [AUC 6] according to local practice IV on day 1) alternating with erlotinib 150 mg orally on days 2 through 15 every 3 weeks for four cycles, followed by erlotinib 150 mg orally daily until PD occurred. Patients were evaluated every 6 weeks by chest x-ray or computed tomography (CT) scan for PD. After PD, patients were treated at physician's discretion (Fig 1). Ongoing patient follow-up was conducted every 3 months.

Biomarkers

The University of Colorado Cancer Center (UCCC, Aurora, CO) received tumor samples from sites to assess EGFR IHC and FISH. UCCC performed quality-control assessments before the analyses to ensure sufficient tumor tissue. With consent, the remnant tissue was used for *EGFR* mutation testing by Genzyme Genetics (Westborough, MA) and *KRAS* mutation analysis by OSI Pharmaceuticals (Boulder, CO). IHC was assessed for E-cadherin and vimentin by OSI Pharmaceuticals.

EGFR IHC

Protein expression for EGFR by IHC was assayed with the Dako (Carpentaria, CA) EGFR PharmDX kit. For the purpose of eligibility, positive EGFR IHC was defined by greater than 10% positive cells assessed by two independent reviewers.¹⁰ In cases of discrepancies, the final score was based on a consensus meeting.

EGFR FISH

FISH analysis was performed according to previously published methods.^{11,12} Samples identified with *EGFR* high polysomy (> four copies of the *EGFR* gene present in 40% to 100% cells) or with *EGFR* gene amplification

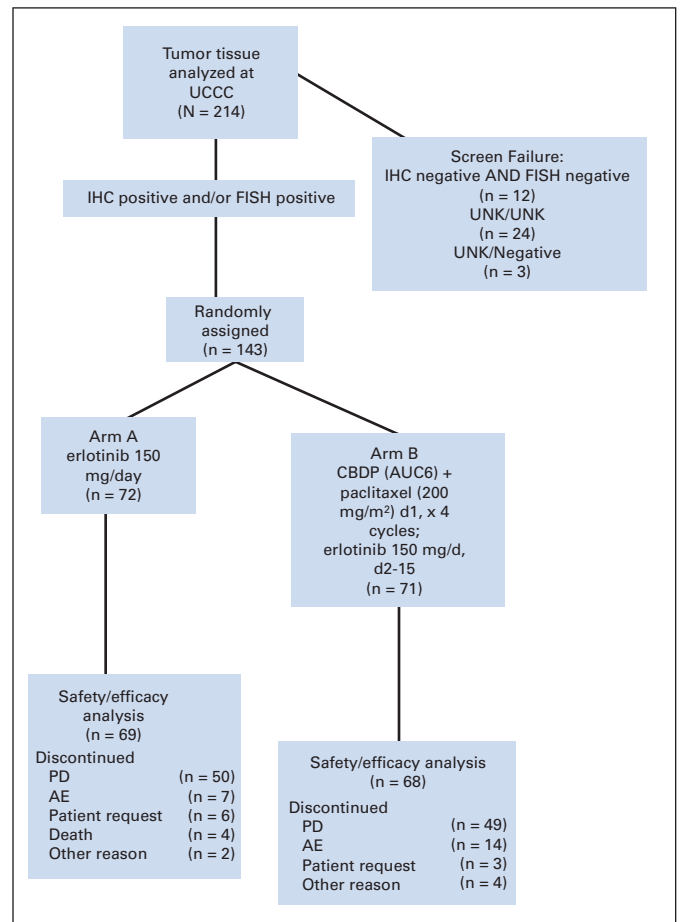


Fig 1. CONSORT diagram. AUC, area under the curve; AE, adverse event; CBDP, carboplatin; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; PD, progressive disease; UCCC, University of Colorado Cancer Center; UNK, unknown.

(gene/chromosome ratio > two or ≥ 15 gene copies in $\geq 10\%$ cells) were considered positive for copy number gain (FISH positive). All other samples were considered FISH negative. The FISH assessment was performed by two independent reviewers, and discrepant assessments were solved by consensus discussion.

EGFR Mutation

EGFR exons 18 through 21 were amplified by polymerase chain reaction (PCR) at Genzyme Genetics according to their standard procedure for *EGFR* mutational analysis. The resultant PCR fragments were sequenced by using BigDye version 1 and 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA). *EGFR* activating mutations were noted by deletions on exon 19 or L858R mutations on exon 21. Patients with other mutations or deletions were classified wild type (WT) for analyses.

KRAS Mutation, E-Cadherin, and Vimentin

The DNA isolated for *EGFR* mutational analysis was used for *KRAS* mutational analysis in codons 12 and 13. The protein expression of E-cadherin was assessed by IHC with antibody H-108 (Santa Cruz Biotechnology No. 7870, Santa Cruz, CA). The assessment was considered high when at least 40% of the cells stained with intensity 2 or 3. The vimentin status was determined by IHC with antibody V9 (Dako No. M0725). The results were considered high when there was at least 10% staining of any intensity.

Statistical Analysis

This was a pick-the-winner, phase II design that was not adequately powered to test for treatment differences, as proposed by Simon et al¹³ Both

treatment arms were considered experimental, and the treatment arm with the numerically superior PFS was to be considered for testing in future studies.

The sample size was based on the ability to detect, with a one-sided α of .05, an improvement in the 6-month PFS rate from an historical 45% with standard first-line platinum-based therapy to a hypothesized 60%, which would be a clinically meaningful improvement.^{4,5} PFS was defined as the time from random assignment until occurrence of documented radiologic and/or symptomatic PD according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.0, or until death in the absence of progression.¹⁴ Patients who did not experience progression were censored on the last day known to be free of progression by objective tumor measurements. Patients who received other therapy before documented PD were censored on the day subsequent therapy started. Survival was defined as time from random assignment until documented death. Patients who were still alive were censored on the last day known to be alive.

PFS and OS analyses included patients who received any study therapy. The 6-month PFS rates with 90% CIs were calculated for each treatment arm, and Kaplan-Meier estimates of PFS and OS were constructed for each treatment arm. In each arm, the 6-month PFS rate was compared with the historical control of 45%. Analyses of RR included patients who received any study therapy and had measurable disease.

Kaplan-Meier estimates of PFS were calculated for each biomarker level (positive ν negative or mutation ν WT) within each treatment arm. Log-rank analyses were performed to test for significant difference between biomarker levels. All *P* values presented are for exploratory purposes. RR and disease control rates (DCRs) were compared between the two groups with two-sided Fisher's exact tests. A *P* value \leq .05 was considered statistically significant.

RESULTS

Patient Characteristics and Tumor Samples

Key patient characteristics and demographics were balanced between arms (Appendix Table A1, online only). Two-hundred forty patients with advanced NSCLC were screened, and formalin-fixed, paraffin-embedded biopsies were obtained in 214 patients (Fig 1). EGFR IHC and/or FISH results were obtained for 190 samples (89%); 24 (11%) failed the quality control analysis (eg, insufficient tissue for analysis) and were not evaluated. At least one of the two EGFR tests was positive in 175 samples (92%); 12 (6%) were negative for both assays; and three had combinations of negative and unknown results. Between March 2007 and December 2008, 143 patients were eligible and randomly assigned; 92% were positive by IHC, and 54% were positive by FISH (Table 1); 45% were positive by both IHC and FISH.

Seventy-two patients were randomly assigned to erlotinib, and 71 patients were randomly assigned to chemotherapy plus erlotinib; 137 patients were included in the efficacy and safety analyses. Six patients did not receive study drug; three were in the erlotinib arm, and three were in the CT plus erlotinib arm.

The 214 tumor tissue samples consisted of primary lung lesions ($n = 145$ [67%]), metastatic sites ($n = 55$ [26%]), and tumor from an unknown location ($n = 14$ [7%]). Biomarker results are listed in Table 1. The average time from receipt of tissue at the central lab to biomarker results being provided to the treatment site was 4 working days (range, 1 to 9 days).

EGFR mutation results were obtained from 119 patients (83%), and activating EGFR mutations were found in 16 patients (11%; $n = 11$, exon-19 deletions; $n = 5$, exon-21 L858R). No difference in distribution between the treatment arms was seen. Two patients had concurrent L858R activating mutation and T790M-acquired resistance mutation. EGFR activating mutations were higher among women (16% ν 6% in men), adenocarcinoma histology (15% ν 0% in

Table 1. Biomarker Results On the Basis of Treatment Arm and Key Patient Characteristics

Biomarker Result	% of Total Patients by Treatment Arm		
	Erlotinib (n = 72)	CP + Intercalated Erlotinib (n = 71)	Total (N = 143)
IHC result			
Positive	93	92	92
Negative	4	8	6
FISH result			
Positive	54	54	54
Negative	43	46	45
EGFR mutation result			
Mutation	18	17	17
Activating mutation	12	10	11
Exon 19 deletion	11	4	8
Exon 21 L858R mutation	1	6	3
Other mutation	6	7	6
No mutation	67	65	66
KRAS mutation result			
Mutation	18	23	20
No mutation	75	73	74
E-cadherin			
High	36	30	33
Low	33	38	36
Vimentin			
High	29	17	23
Low	40	48	44

Abbreviations: CP, carboplatin/paclitaxel; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

others), Asian ethnicity (38% ν 8% in non-Asians), and never smokers (28% ν 5% in former smokers and 4% in current smokers).

KRAS mutation analysis was performed in 135 patients, and 29 (20%) had mutations. No patient had both EGFR and KRAS mutation. KRAS mutation rates were highest in current smokers (40% ν 22% in former and 8% in never smokers).

EGFR FISH was performed in 141 patients and was positive in 77 patients (54%). No difference in the distribution of EGFR FISH positivity was seen regarding sex, histology or smoking status. EGFR IHC was positive in 132 (92%) of 141 patients; no difference was associated with sex, histology or smoking status. E-cadherin expression was high in 47 (48%) of 98 patients, and vimentin was high in 33 (24%) of 96 patients.

The associations among EGFR mutation, KRAS mutations, and EGFR FISH are shown in Figure 2 for the 119 patients evaluable for FISH, EGFR mutation, and KRAS mutation. Of the 66 EGFR FISH-positive tumors, 10 had KRAS mutations. Among 16 tumors with EGFR activating mutations, 13 were EGFR FISH positive.

Treatment Administration

Patients in the erlotinib arm received a median of 10.3 weeks of treatment (range, 1.1 to 125.7 weeks). Patients in the chemotherapy plus erlotinib arm received a median of 9.8 weeks (range, 0.1 to 95.6 weeks).

Efficacy

PFS. Kaplan-Meier curves of PFS are shown in Figure 3. For the overall population, the curves favored the chemotherapy plus

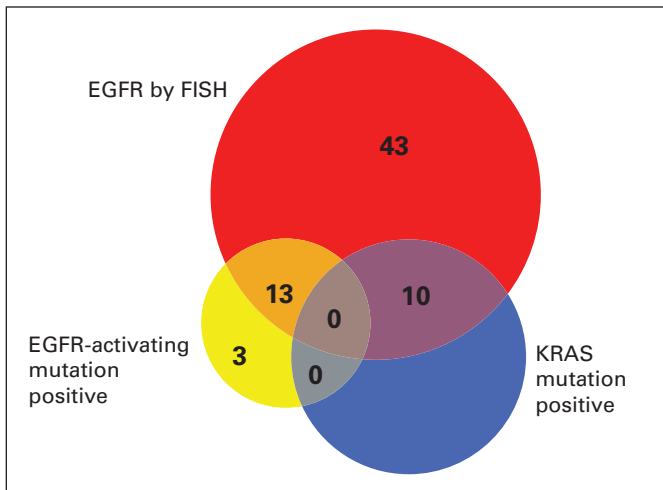


Fig 2. Thirty-six patients were fluorescent in situ hybridization negative, *KRAS* wild type (WT), and *EGFR* WT.

erlotinib arm during the first 6 months and then crossed to favor the erlotinib arm. The 6-month PFS rate was 31% (90% CI, 22% to 40%) in the erlotinib arm, and it was 26% (90% CI, 17% to 36%) with chemotherapy plus erlotinib. The 6-month PFS rate in each arm was less than the historical control of 45% (erlotinib arm, $P = .011$; chemotherapy plus erlotinib arm, $P = .001$). The median PFS times were 2.69 months and 4.57 months within the two groups, respectively (Table 2). The 6-month PFS rate for patients with *EGFR* activation mutations was considerably better in the erlotinib arm than in the chemotherapy plus erlotinib arm (89% v 42%, respectively), as was the median PFS (18.2 months v 4.9 months, respectively).

Within the erlotinib arm, patients with *EGFR* activating mutations had a 6-month PFS rate of 89% compared with 24% for the *EGFR* WT patients ($P < .001$). In the chemotherapy plus erlotinib arm, patients with *EGFR* mutations had a 6-month PFS rate of 42% compared with 28% for the *EGFR* WT patients ($P = .502$).

For the *EGFR* FISH-positive patients, the 6-month PFS rate was 39% in the erlotinib arm, and it was 23% in the chemotherapy plus erlotinib arm; the PFS rates were 22% and 30%, respectively, for the FISH-negative group. In the erlotinib arm, among the *EGFR* WT patients, the 6-month PFS rate for the FISH-positive group was 27%, and it was 21% for the FISH-negative group ($P = .520$).

EGFR IHC did not confer any difference in the 6-month PFS rate (Table 2). *KRAS* mutation appeared to have a negative effect on 6-month PFS rate for patients in both arms, although the results were not statistically significant (Table 2). For E-cadherin or vimentin expression, no differential association was seen (Table 2).

Tumor Response

The overall response rate (RR; ie, CR + PR) was 11.6% in the erlotinib arm, and it was 22.4% in the chemotherapy plus erlotinib arm (Table 3). For patients with activating *EGFR* mutation, the RR was 67% in the erlotinib arm and it was 33% in the chemotherapy plus erlotinib arm. For *EGFR* WT patients, the RRs were 0% and 23% in the two arms, respectively. The DCR was 100% in patients who were *EGFR* activating mutation positive, and it was 36% in *EGFR* WT patients in the erlotinib arm ($P = .0004$) compared with 67% for mutation-positive patients and 68% for WT patients in the chemo-

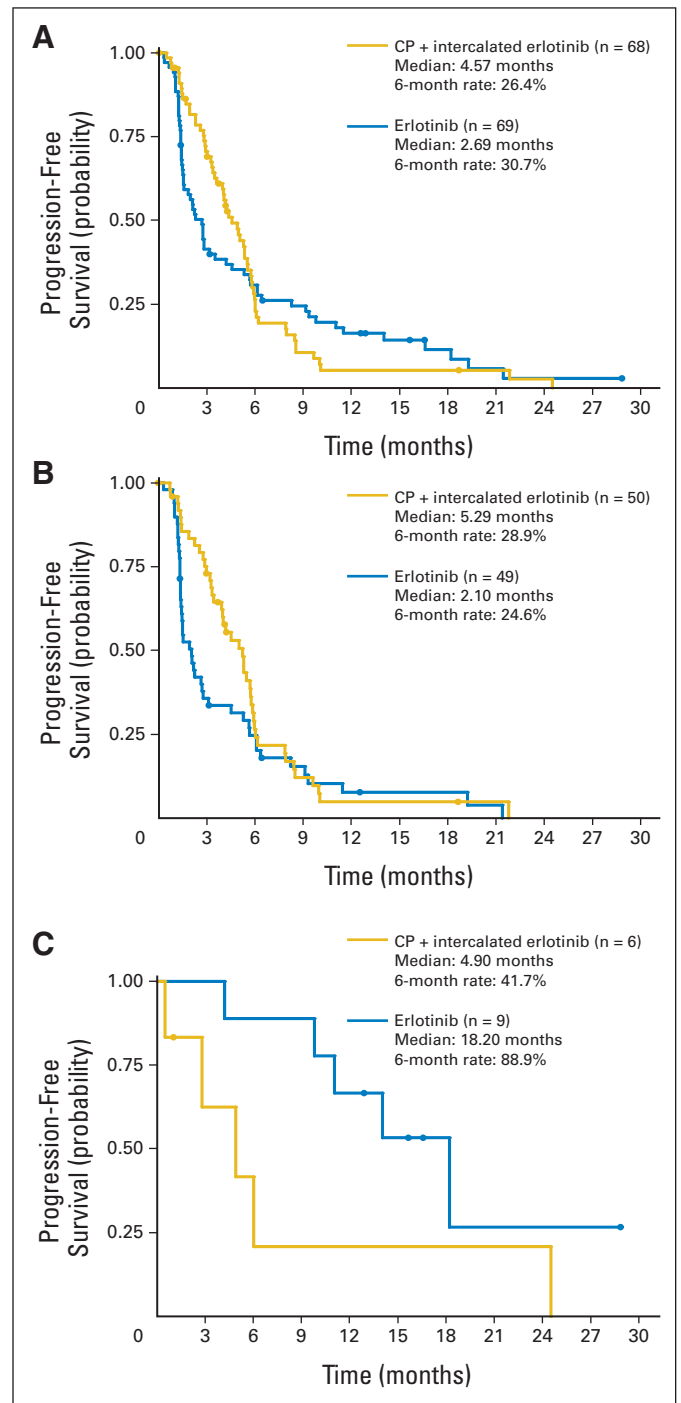


Fig 3. Kaplan-Meier plots of progression-free survival. (A) All patients; (B) *EGFR* wild-type patients; (C) *EGFR* mutant patients. CP, carboplatin/paclitaxel.

therapy plus erlotinib arm ($P = 1.0$). *EGFR* FISH-positive patients had a numerically higher RR (18.9% in the erlotinib arm and 26% in the chemotherapy plus erlotinib arm) compared with the *EGFR* FISH-negative patients (3% in the erlotinib arm and 19% in the chemotherapy plus erlotinib arm; Table 3). *KRAS* mutations had a trend toward a negative effect on RR and DCR when these patients were compared with patients who were *KRAS* WT (erlotinib: RR 0% v 16% [$P = .1908$]; DCR 31% v 53% [$P = .2168$]; and chemotherapy plus

Table 2. Analyses of PFS and OS for Biomarker Subsets

Biomarker Subset	All Patients		EGFR WT Only	
	Erlotinib	CP + Erlotinib	Erlotinib	CP + Erlotinib
EGFR FISH positive				
No.	37	35	23	27
Median PFS	2.76	5.06	2.10	5.29
6-month PFS rate	39.2	23.4	27.6	21.7
12-month OS rate	62.2	54.7	57.3	60.1
EGFR FISH negative				
No.	30	33	26	23
Median PFS	2.27	4.17	1.91	4.24
6-month PFS rate	22.2	29.8	22.0	38.1
12-month OS rate	58.3	38.4	55.5	49.5
<i>P</i> for PFS of positive v negative*	.075	.778	.492	.652
KRAS mutation				
No.	13	15	11	12
Median PFS	2.23	2.96	2.23	2.30
6-month PFS rate	11.5	8.6	NC	11.4
12-month OS rate	40.4	53.3	47.7	58.3
KRAS WT				
No.	51	51	38	38
Median PFS	3.15	4.90	1.97	5.36
6-month PFS rate	38.2	31.7	27.3	33.9
12-month OS rate	63.1	44.3	57.9	53.5
<i>P</i> for PFS of mutated v WT*	.078	.078	.550	.092
E-cadherin positive: high				
No.	25	21	19	15
Median PFS	2.76	4.90	2.69	5.52
6-month PFS rate	28.0	21.4	21.1	31.4
12-month OS rate	58.8	53.1	55.9	65.2
E-cadherin negative: low				
No.	22	26	18	21
Median PFS	1.54	5.06	1.45	5.06
6-month PFS rate	33.2	31.0	24.2	27.3
12-month OS rate	75.6	31.4	69.6	34.4
<i>P</i> for PFS of high v low*	.794	.725	.495	.836
Vimentin positive: high				
No.	20	12	15	8
Median PFS	1.48	5.78	1.41	6.01
6-month PFS rate	27.1	41.6	7.5	53.6
12-month OS rate	58.2	50.3	50.3	75.0
Vimentin negative: low				
No.	28	33	22	27
Median PFS	2.50	4.90	2.27	5.29
6-month PFS rate	27.5	22.0	26.0	23.1
12-month OS rate	66.5	38.7	66.1	41.6
<i>P</i> for PFS of high v low*	.757	.163	.287	.058

Abbreviations: PFS, progression-free survival; OS, overall survival; WT, wild type; CP, carboplatin/paclitaxel; FISH, fluorescent in situ hybridization; NC, not calculated.

**P* values are from the log-rank test comparing the erlotinib and CP + erlotinib curves.

erlotinib: RR 20% v 24% [*P* = 1.0]; DCR, 53% v 78% [*P* = .0977]). For EGFR IHC, E-cadherin status, and vimentin status, no statistically significant differences were seen for RR.

OS

Among 137 patients assessed for survival, the median survival time was 16.7 months in the erlotinib arm, and it was 11.43 months in the chemotherapy plus erlotinib arm. The 12-month survival rates

Table 3. Response by Biomarker Status

Factor	% of Patients by Response and Treatment Arm			
	CR + PR		CR + PR + SD	
	Erlotinib (n = 69)	CP + Intercalated Erlotinib (n = 67)*	Erlotinib (n = 69)	CP + Intercalated Erlotinib (n = 67)*
Overall	11.6	22.4	46.4	71.6
EGFR by IHC status				
Positive	9.4	21.3	45.3	72.1
Negative	33.3	33.3	66.7	66.7
EGFR by FISH status				
Positive	18.9	25.7	54.1	74.3
Negative	3.3	18.8	36.7	68.8
EGFR mutation status				
Mutation	53.8	36.4	84.6	81.8
Activating mutation	66.7	33.3	100.0	66.7
Other mutation	25.0	40.0	50.0	100.0
No mutation	0	22.7	35.6	68.2
KRAS mutation status				
Mutation	0	20.0	30.8	53.3
No mutation	15.7	24.0	52.9	78.0
E-cadherin				
High	8.0	28.6	52.0	76.2
Low	18.2	16.0	36.4	56.0
Vimentin				
High	15.0	27.3	40.0	100.0
Low	10.7	21.2	42.9	57.6

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; CP, carboplatin/paclitaxel; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

*One patient on the CP + intercalated erlotinib arm had no measurable disease at baseline and was nonevaluable for response.

were 59% and 46%, respectively (Table 2; Fig 4). For patients with activating *EGFR* mutations, the 12-month OS rate was 100% in the erlotinib arm, and it was 41.7% in the chemotherapy plus erlotinib arm. However, in the *EGFR* WT patients, survival curves were nearly overlapping, and the median survival times were 15.6 months and 13.3 months in the erlotinib and the chemotherapy plus erlotinib arms, respectively (Fig 4).

For the EGFR FISH-positive patients no statistically difference was seen between the two treatment arms (12-month OS rates of 62% for erlotinib and 55% for chemotherapy plus erlotinib). In the FISH-negative group, the 12-month OS rates were 56.5% with erlotinib and 38.4% with chemotherapy plus erlotinib (Table 2). For the EGFR IHC-positive patients, the 12-month OS rates were 56.8% in the erlotinib arm and 40.1% in the chemotherapy plus erlotinib arm. No difference in survival was seen among patients within the same treatment arm for *KRAS* mutation versus WT, E-cadherin high versus low expression, or vimentin high versus low expression (Table 2).

Toxicity. The most common adverse event was skin rash (81% [grades 3 to 4, 9%] in erlotinib arm and 76% [grades 3 to 4, 4%] in the chemotherapy plus erlotinib arm; Table A2). In the chemotherapy plus erlotinib arm, 10 patients (15%) had chemotherapy adjustments as a result of hematologic toxicity, and 29 patients (43%) had them as a result of nonhematologic toxicity. There was at least one dose interruption of erlotinib in 17 patients (25%) in the erlotinib arm and in 23 patients (34%) in the chemotherapy plus erlotinib arm.

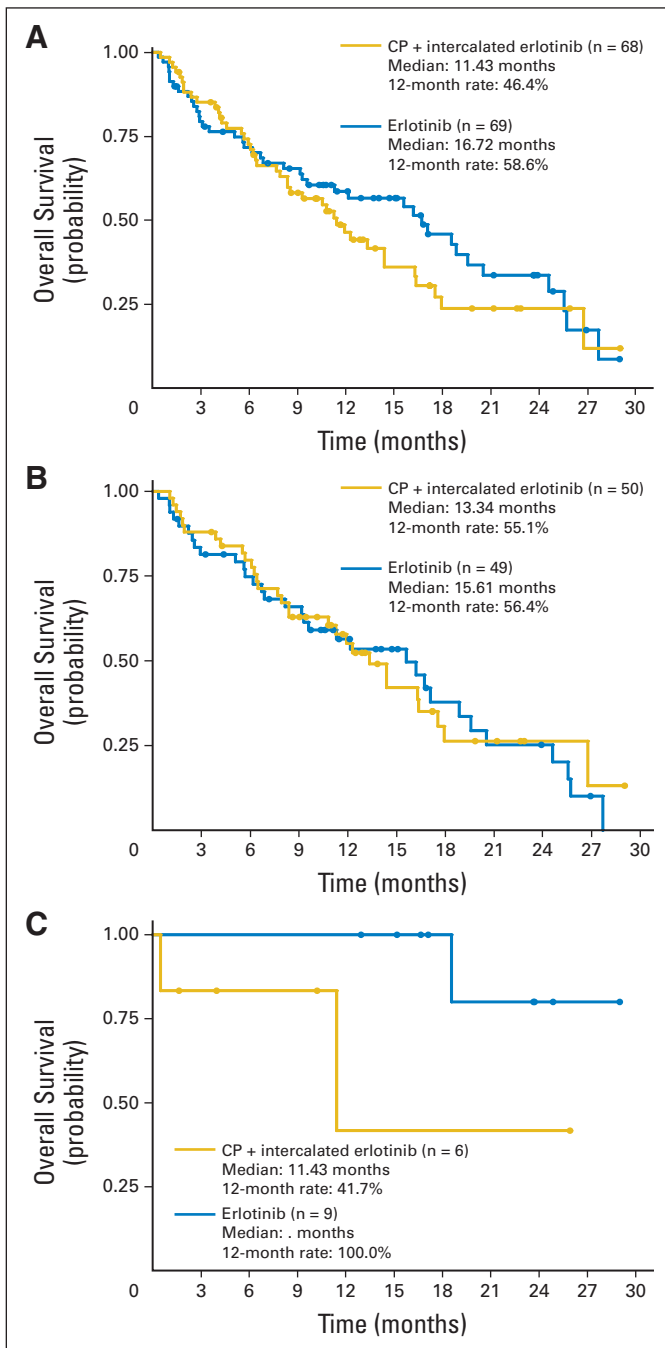


Fig 4. Kaplan-Meier plots of overall survival. (A) All patients; (B) EGFR wild-type patients; (C) EGFR mutant patients. CP, carboplatin/paclitaxel.

DISCUSSION

Personalized medicine requires molecular analyses of tumor tissue obtained before therapy to select the best treatment. One goal of this study was to determine whether molecular tests could be performed on lung cancer samples from untreated patients with advanced-stage NSCLC in a clinically relevant time frame (defined in this study as < 5 working days). We obtained tissue from 215 (89.6%) of 240 screened patients without additional rebiopsy. Of these, 11% failed quality

control evaluation. Thus, molecular results were available on 80% of the patients, demonstrating that molecular phenotyping can be done in the majority of patients in a reasonable time frame to select therapy. The primary goal was to evaluate treatment outcomes from intercalating erlotinib with chemotherapy and erlotinib alone. In this EGFR-selected population, the intercalated therapy provided similar outcomes to erlotinib alone on the basis of the primary end point of 6-month PFS. Neither treatment arm exceeded the historical 6-month PFS rate of 45%.^{4,5}

An exploratory goal was to determine whether erlotinib alone could be superior to intercalated therapy in any of the biomarker-selected patients. Patients with activating *EGFR* mutations treated with erlotinib alone had superior RRs, superior PFS, and superior OS compared with the intercalated therapy arm. The favorable response rates and outcome for patients with advanced NSCLC who had *EGFR* mutations and who were treated with EGFR TKIs alone are consistent with studies evaluating gefitinib in untreated patients with advanced-stage NSCLC^{7,15,16} and with the OPTIMAL study, which demonstrated superior PFS with erlotinib alone compared with chemotherapy in patients with *EGFR* mutations.¹⁶ In patients with *EGFR* mutations, the lower RR and shorter PFS with intercalated therapy suggest antagonism between the treatments.^{3,8} In patients with *EGFR* WT, the results with intercalated therapy were similar to those reported with chemotherapy alone.^{4,5}

In studies of erlotinib in later lines of therapy, patients with *EGFR* WT treated with erlotinib had a superior survival compared with placebo.^{1,2} Thus, a remaining question is whether a single biomarker or combination of biomarkers will help to select patients with *EGFR* WT tumors for EGFR TKI therapy in the first line and beyond. This trial does not support use of erlotinib or chemotherapy plus erlotinib in the first-line setting in *EGFR* WT patients who could be selected by any other analyzed biomarker, including *EGFR* FISH or *KRAS* mutations. When the *EGFR*-mutated patients are excluded from the FISH-positive analysis and from the *KRAS* WT analysis, there remains no striking difference in outcome between those treated with erlotinib or intercalated therapy on the basis of FISH or *KRAS* status. Our finding is supported by the results from Cancer and Leukemia Group B study CALGB 30406, in which no difference between erlotinib alone or chemotherapy plus erlotinib was found in never smokers or light smokers who had lung adenocarcinomas with high response and by the positive outcome in patients with *EGFR* mutations treated with erlotinib alone, which support the use of an EGFR TKI alone as first-line therapy in patients with NSCLC who have *EGFR* mutations.¹⁷

In summary, this study could not demonstrate any benefit of combining chemotherapy and intercalated EGFR TKI in patients with advanced NSCLC. The study demonstrated the feasibility of a prospective, multi-institutional biomarker study in advanced NSCLC and supports the importance of determining the *EGFR* mutation status of patients with advanced NSCLC before initial therapy.

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.

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