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ORIGINAL REPORT

Randomized, Placebo-Controlled, Phase II Study of Sequential Erlotinib and Chemotherapy As First-Line Treatment for Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
This study investigated whether sequential administration of erlotinib and chemotherapy improves clinical outcomes versus chemotherapy alone in unselected, chemotherapy-naïve patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Previously untreated patients (n = 154) with stage IIIB or IV NSCLC and Eastern Cooperative Oncology Group performance status of 0 or 1 were randomly assigned to receive erlotinib (150 mg/d) or placebo on days 15 to 28 of a 4-week cycle that included gemcitabine (1,250 mg/m^2 days 1 and 8) and either cisplatin (75 mg/m^2 day 1) or carboplatin (5 × area under the serum concentration-time curve, day 1). The primary end point was nonprogression rate (NPR) at 8 weeks. Secondary end points included tumor response rate, NPR at 16 weeks, duration of response, progression-free survival (PFS), overall survival (OS), and safety.

Results
The NPR at 8 weeks was 80.3% in the gemcitabine plus cisplatin or carboplatin (GC) -erlotinib arm (n = 76) and 76.9% in the GC-placebo arm (n = 78). At 16 weeks, the NPR was 64.5% for GC-erlotinib versus 53.8% for GC-placebo. The response rate was 35.5% for GC-erlotinib versus 24.4% for GC-placebo. PFS was significantly longer with GC-erlotinib than with GC-placebo (adjusted hazard ratio, 0.47; log-rank P = .0002; median, 29.4 *v* 23.4 weeks); this benefit was consistent across all clinical subgroups. There was no significant difference in OS. The addition of erlotinib to chemotherapy was well tolerated, with no increase in hematologic toxicity, and no treatment-related interstitial lung disease.

Conclusion
Sequential administration of erlotinib following gemcitabine/platinum chemotherapy led to a significant improvement in PFS. This treatment approach warrants further investigation in a phase III study.

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INTRODUCTION

Advanced-stage, non–small-cell lung cancer (NSCLC) is one of the most life-threatening malignancies. Platinum-based doublet chemotherapy was established in the 1990s as standard first-line therapy for advanced NSCLC. Since then, there has been limited success in improving on the typical median overall survival (OS) period of 8 to 11 months with cytotoxic drugs alone.[1,2]

Erlotinib is a potent, orally active, epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR TKI) that is approved worldwide for treatment of advanced NSCLC following failure of chemotherapy. In the phase III BR.21 study, erlotinib significantly improved OS and progression-free survival (PFS) versus placebo and also provided significant symptom and quality-of-life benefits.[3,4] The results of this study have been confirmed in clinical practice in a large (> 7,000 patients) phase IV study.[5]

The potential for combining EGFR TKIs with cytotoxic drugs was initially investigated in four randomized phase III trials.[6-9] In these studies, concurrent administration of erlotinib or gefitinib with standard platinum-doublet chemotherapy did not improve survival compared with chemotherapy alone. Preclinical evidence suggests that a possible reason for the lack of success in these studies was potential antagonism between the constituents of

the combination therapy. EGFR TKIs induce G_1-phase cell cycle arrest, which protects cells from the cytotoxic effects of cell cycle phase–dependent chemotherapeutic agents.[10,11] In contrast, sequential administration of EGFR TKIs following chemotherapy, thus achieving pharmacodynamic separation of these two therapeutic approaches, has been shown to provide greater efficacy than concurrent administration.[12-14] Early clinical evidence also supports this hypothesis, with sequential administration of docetaxel or pemetrexed followed by erlotinib resulting in promising activity.[15,16]

The multicenter, randomized phase II First-Line Asian Sequential Tarceva and Chemotherapy Trial (FAST-ACT) was conducted to evaluate the efficacy and tolerability of sequential scheduling of erlotinib with chemotherapy in patients with advanced NSCLC.

PATIENTS AND METHODS

Patients

Patients age ≥ 18 years, with histologically documented stage IIIB or IV NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumors)[17] were eligible. Exclusion criteria included prior systemic chemotherapy for advanced NSCLC, uncontrolled symptomatic brain metastases, prior exposure to anti-ErbB agents, any unstable medical condition, and inadequate renal, hepatic, or hematologic function. All patients provided written informed consent; consent to tumor sample collection and biomarker analysis was optional. The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines, with approval obtained from each center's independent ethics committee.

Study Design

Patients were randomly assigned in a 1:1 ratio to oral erlotinib 150 mg/d or placebo on days 15 to 28 of a 4-week cycle including platinum-based doublet chemotherapy: gemcitabine (1,250 mg/m^2 days 1 and 8) and either cisplatin (75 mg/m^2 day 1) or carboplatin (5 × area under the serum concentration-time curve, day 1; sequential combination phase). The choice of platinum drug was made by each center before initiation of the study; all patients recruited within a center received the same chemotherapy regimen. In the absence of disease progression, chemotherapy was continued for a maximum of six cycles, after which time patients continued to receive erlotinib or placebo monotherapy until disease progression or unacceptable toxicity (maintenance phase). On disease progression, patients in the gemcitabine plus cisplatin or carboplatin (GC) –placebo arm were offered optional second-line erlotinib monotherapy. The choice of second-line therapy was at the investigator's discretion. Randomization was stratified according to center, disease stage (IIIB/IV), histology (adenocarcinoma/other), and smoking status (never/former/current) using a minimization algorithm with a random element incorporated into the assignment.[18]

Assessments

Tumor response (according to RECIST) was assessed via computed tomography or magnetic resonance imaging scan between days 22 and 28 of chemotherapy cycles 2, 4, and 6, and every 8 weeks following completion of chemotherapy. Adverse events (AEs) were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Where possible, diagnostic tumor specimens were collected for biomarker analysis to determine any correlation with treatment outcome.

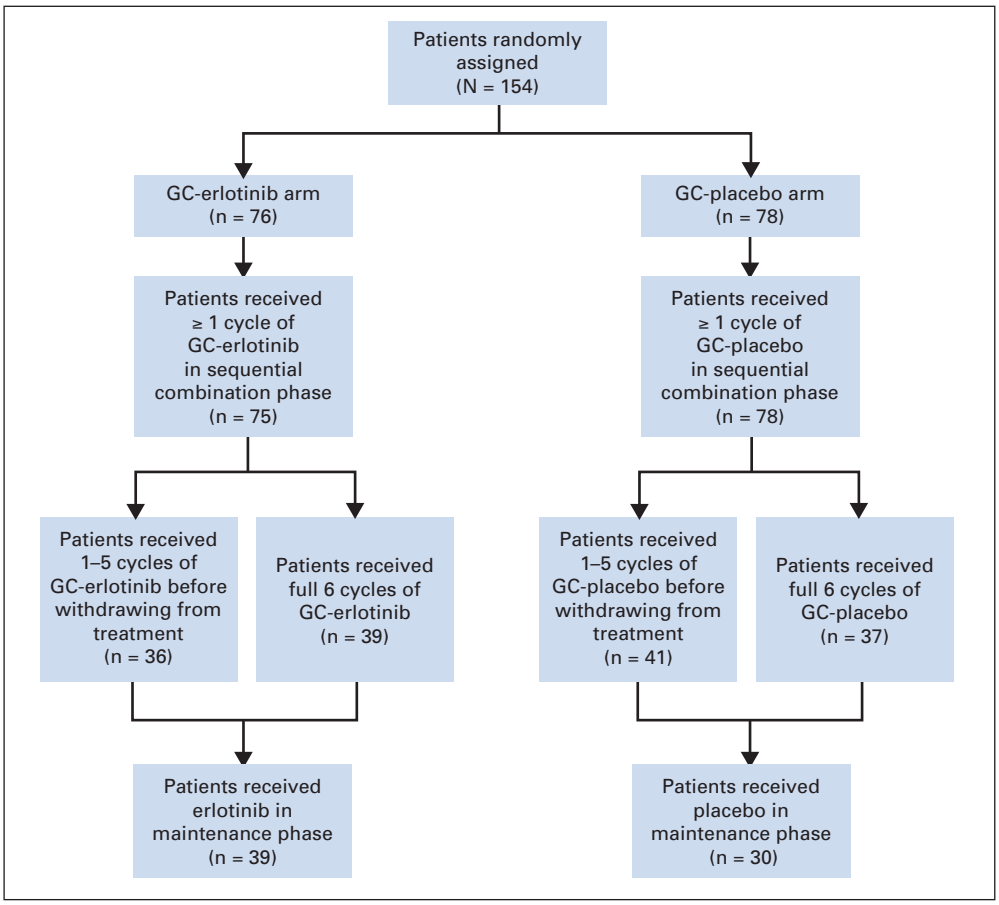

Fig 1. Patient disposition. GC, gemcitabine plus cisplatin or carboplatin.

Molecular Analyses

Gene sequencing was performed at the Roche Centre for Medical Genomics (Basel, Switzerland), and other histopathologic and molecular analyses were conducted at HistoGeneX (Antwerp, Belgium), using technically validated assays, as described previously.[19]

Samples were classified as *EGFR* mutation–positive if exon 19 deletions and/or L858R mutations (exon 21) were detected. *KRAS* mutation–positive status was assigned to samples with mutations in codons 12, 13, or 61. Samples were classified as EGFR immunohistochemistry–positive if there was membrane staining of EGFR in ≥ 10% tumor cells, and as *EGFR* fluorescent in situ hybridization–positive in cases of high polysomy or gene amplification.[20]

Statistical Analysis

The primary end point was nonprogression rate (NPR) at 8 weeks (complete response, partial response, or stable disease, where stable disease was maintained > 8 weeks). If the NPR is 60% in the GC-erlotinib group and 45% in the GC-placebo group, then with a probability of 80%, the observed difference in NPR at 8 weeks would be greater than 8.5%. This required enrollment of 150 patients. Secondary end points included NPR at 16 weeks, objective response rate (ORR; complete response or partial response), duration of response, PFS, and OS.

The cutoff for the final analysis was 18 months after the last patient was randomly assigned. For NPR and ORR, a stratified logistic regression model, adjusting for the stratification factors at randomization, was used to calculate the odds ratio (OR) for treatment. Kaplan-Meier curves were used to describe time-to-event end points, and a two-sided log-rank test was used to compare treatment groups. The Cox proportional hazards model, adjusting for the stratification factors at randomization, was used to calculate the hazard ratio (HR) for treatment. For duration of response, the Cox model only included treatment. ORR and PFS were analyzed by predefined subgroups, including disease stage, smoking status, histology, sex, and age group.

Table 1. Patient and Disease Characteristics At Baseline

Characteristic	GC-Erlotinib (n = 76) No.	%	GC-Placebo (n = 78) No.	%
Age, years				
Median	57.5		57.0	
Range	33 to 79		27 to 79	
Sex				
Male	54	71	54	69
Female	22	29	24	31
Disease stage				
IIIB	13	17	16	21
IV	63	83	62	79
Histology				
Adenocarcinoma	51	67	52	67
Other	25	33	26	33
Smoking status				
Current	33	43	36	46
Former	19	25	14	18
Never	24	32	28	36
ECOG PS				
0	29	38	23	29
1	47	62	55	71
Ethnicity				
Asian	71	93	74	95
Caucasian	5	7	4	5
Prior treatment for NSCLC*				
Radiotherapy	31	41	27	35
Surgery	9	12	6	8
Chemotherapy	2	3	3	4

Abbreviations: GC, gemcitabine plus cisplatin or carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small-cell lung cancer.

*Adjuvant or neoadjuvant chemotherapy for nonmetastatic disease was permitted if completed ≥ 6 months prior to starting study treatment.

RESULTS

Patients

Between August 2006 and April 2007, 154 patients were enrolled at 19 centers in seven Asian Pacific countries. The data cutoff for this report was October 2008. A total of 76 patients were randomly assigned to GC-erlotinib and 78 to GC-placebo (Fig 1). Baseline demographics and disease characteristics were well balanced between treatment arms (Table 1).

Study Treatment

Fifty-five patients in each arm received four to six cycles of chemotherapy (74% for GC-erlotinib, 70% for GC-placebo). The mean dose intensity for erlotinib and placebo in the sequential combination phase was 147.9 and 149.7 mg/d, respectively. One patient withdrew consent after random assignment and did not receive any study treatment. Patients who did not progress during the sequential combination phase received further erlotinib (53%; n = 39) or placebo (38%; n = 30) as maintenance therapy. At the time of reporting, the median number of days on maintenance treatment was 114 for erlotinib and 59 for placebo, with a mean dose intensity of 146.0 and 149.7 mg/d, respectively.

Dose reductions for erlotinib were required in three (4%) patients (all to 100 mg/d) during the sequential combination phase, and in five (13%) patients who entered the maintenance phase. There were no dose reductions for placebo in either phase of the study. Dose interruptions, all lasting less than 1 week were also uncommon. During the sequential combination phase, dose interruptions were required in three (4%) patients in the GC-erlotinib arm and two (3%) in the GC-placebo arm. Dose interruptions were required for five (13%) patients in the GC-erlotinib arm who entered the maintenance phase and no patients in the GC-placebo arm.

Efficacy

Efficacy analyses were based on the intent-to-treat population, which included all randomly assigned patients (n = 154). The NPR at 8 weeks was 80.3% in the GC-erlotinib arm and 76.9% in the GC-placebo arm (adjusted OR, 1.33; 95% CI, 0.57 to 3.10; $P = .51$). At 16 weeks, the difference in NPR between arms was 11% in favor of GC-erlotinib (64.5% *v* 53.8%; adjusted OR, 1.70; 95% CI, 0.84 to 3.41; $P = .14$). The tumor response rate was higher in the GC-erlotinib arm (35.5% *v* 24.4%; adjusted OR, 1.75; 95% CI, 0.86 to 3.57; $P = .12$). Planned subgroup analyses showed that the benefit in tumor response rate with erlotinib was consistent across all clinical subgroups except former smokers (Table 2). The duration of response was significantly longer in the GC-erlotinib arm (HR, 0.40; 95% CI, 0.20 to 0.79; log-rank $P = .0057$; median, 39.4 *v* 24.1 weeks for GC-placebo). PFS was also significantly longer in the GC-erlotinib arm (adjusted HR, 0.47; 95% CI, 0.33 to 0.68; log-rank $P = .0002$; median, 29.4 *v* 23.4 weeks in GC-placebo arm; Fig 2). Planned subgroup analyses showed that the PFS benefit was consistent across all clinical subgroups (Table 2), with improved PFS in both ever smokers (current and former) and

Table 2. Subgroup Analysis of ORR and PFS

Variable	GC-Erlotinib			GC-Placebo				
	No.	ORR* (%)	Median PFS (weeks)	No.	ORR* (%)	Median PFS (weeks)	PFS Univariate HR	95% CI†
All patients	76	35.5	29.4	78	24.4	23.4	0.47	0.33 to 0.68
Age, years								
< 65	57	36.8	29.4	59	25.4	24.1	0.49	0.33 to 0.74
≥ 65	19	31.6	25.3	19	21.1	16.7	0.72	0.37 to 1.39
Sex								
Male	54	33.3	25.7	54	24.1	19.9	0.52	0.35 to 0.79
Female	22	40.9	37.3	24	25.0	26.6	0.55	0.30 to 1.03
Disease stage								
IIIB	13	38.5	36.0	16	25.0	24.3	0.29	0.11 to 0.76
IV	63	34.9	29.4	62	24.2	22.1	0.57	0.39 to 0.83
Histology								
Adeno	51	35.3	32.1	52	25.0	23.7	0.48	0.31 to 0.74
Nonadeno	25	36.0	23.4	26	23.1	19.6	0.66	0.37 to 1.18
Smoking status								
Current	33	30.3	25.1	36	13.9	17.5	0.58	0.35 to 0.95
Former	19	31.6	31.9	14	35.7	19.4	0.55	0.26 to 1.15
Never	24	45.8	48.1	28	32.1	28.0	0.37	0.20 to 0.71

Abbreviations: ORR, objective response rate; PFS, progression-free survival; GC, gemcitabine plus cisplatin or carboplatin; HR, hazard ratio; Adeno, adenocarcinoma.
*All responses were partial responses.
†The univariate HR for GC-erlotinib compared with GC-placebo was derived from a Cox model including only treatment as a factor; HR < 1 favors erlotinib.

never smokers (Fig 2). There were no significant interactions between treatment arm and any of the baseline characteristics. OS was similar between the two arms (median, 74.1 weeks for GC-erlotinib *v* 75.7 weeks for GC-placebo; adjusted HR, 1.09; 95% CI, 0.70 to 1.69; log-rank $P = .42$). Never smokers (median not reached; lower limit of 95% CI, 85.7 weeks) had longer OS than ever smokers (median, 57.9 weeks; 95% CI, 42.7 to 75.1 weeks), regardless of the treatment received (log-rank $P < .0001$).

Molecular Analyses

A total of 47 (31%) samples were available for molecular analysis. Among evaluable samples, 10 (56%) of 18 were EGFR immunohistochemistry–positive, eight (73%) of 11 were *EGFR* fluorescent in situ hybridization–positive, one (11%) of nine possessed *KRAS* mutations, and seven (41%) of 17 were *EGFR* mutation–positive. Table 3 shows patient demographics and treatment outcomes for those in whom *EGFR* mutation status was determined.

Safety

The safety population included patients who received at least one dose of study medication (n = 153; one patient withdrew consent). One patient was randomly assigned to GC-erlotinib but withdrew consent before receiving any double-blind erlotinib/placebo. Since this patient completed one cycle of chemotherapy, this patient was included in the GC-placebo arm for safety analyses.

Seventy patients in each arm (95% for GC-erlotinib, 89% for GC-placebo) had at least one AE that was considered to be possibly related to study treatment (Table 4). The majority of reported AEs were grade 1 or 2; in the GC-erlotinib and GC-placebo arms, respectively, 32% and 30% had a grade 3 treatment-related AE, and 8% and 9% had a grade 4 treatment-related AE (mostly hematologic toxicity in both arms). The incidence of hematologic AEs was similar across both treatment arms. Skin rash was more common with GC-erlotinib (65% *v* 34% with GC-placebo) but was mostly grade 1 to 2; only 3% of patients in the GC-erlotinib arm had grade 3 rash and none had grade 4 rash. Rash could occur because of gemcitabine or erlotinib or both; although the presentation of the rash produced by these two agents is different, no differentiation was made in data collection. Therefore, it was not possible to analyze any correlation between grade of erlotinib-related rash and clinical outcome.

Eight patients in each arm had at least one treatment-related serious AE; the most common serious AE was anemia, which occurred in four patients in each arm. One grade 5 (fatal) treatment-related AE was observed in the GC-erlotinib arm (bacterial pneumonia) and two were observed in the GC-placebo arm (thrombocytopenia; upper GI bleeding). There were no cases of interstitial lung disease (ILD).

During the sequential combination phase, 35 (47%) patients withdrew from the GC-erlotinib arm and 42 (53%) withdrew from the GC-placebo arm. The principal reason for withdrawal was disease progression (22 and 31 patients in the GC-erlotinib and GC-placebo arms, respectively); seven patients in the GC-erlotinib arm and two in the GC-placebo arm withdrew for toxicity reasons. No patients withdrew as a result of skin rash. Two patients (GC-erlotinib arm) withdrew for safety reasons during the maintenance phase; in both patients, this was considered by the investigator to be unrelated to study treatment.

Subsequent Systemic Anticancer Therapy

Of the 78 patients in the GC-placebo arm, 61 (78%) went on to receive subsequent treatment for NSCLC: 57 (73%) of these patients received optional cross-over erlotinib. Of the 76 patients in the GC-erlotinib arm, 39 (51%) received subsequent treatments for NSCLC; the majority received taxane or pemetrexed. Many patients received several lines of subsequent therapy.

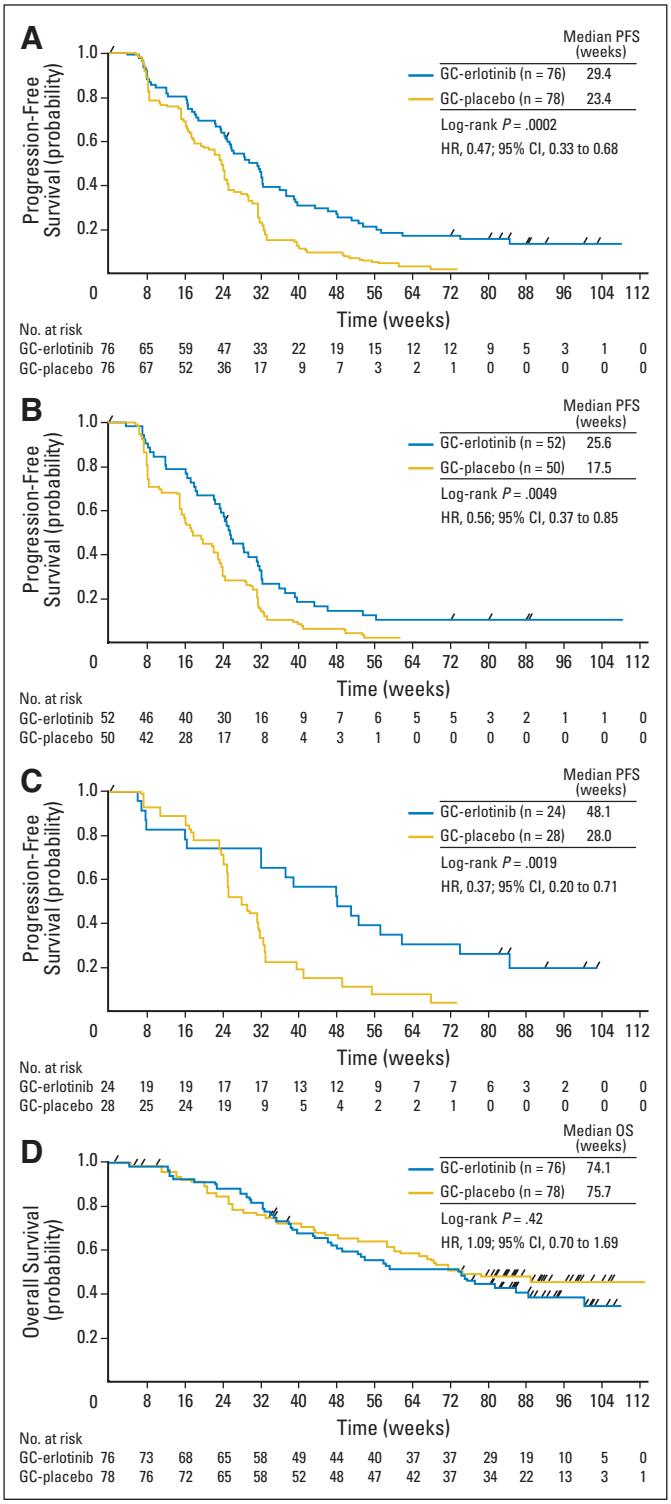

Fig 2. Progression-free survival (PFS) in (A) all patients, in (B) ever smokers, and in (C) never smokers, and (D) overall survival in all patients. GC, gemcitabine plus cisplatin or carboplatin; HR, hazard ratio.

DISCUSSION

To our knowledge, this is the first proof-of-concept, randomized, placebo-controlled phase II study that has demonstrated an improvement in treatment outcomes with sequential combination of erlotinib and cytotoxic chemotherapy. Although the primary end point of NPR at 8 weeks was not met, patients in the erlotinib plus chemotherapy arm had a higher NPR at 16 weeks and obtained a significant 53% improvement in PFS compared with those in the placebo plus chemotherapy arm (HR, 0.47; median, 29.4 *v* 23.4 weeks). The observed PFS benefit with erlotinib was consistent across all predefined clinical subgroups and was statistically significant in some subgroups, despite the small number of patients involved.

Retrospectively, we recognized that the NPR at 8 weeks, which was intended to measure a potential early benefit of sequential combination therapy,[21] was not an adequate primary end point for this study. The consistently higher ORR and longer PFS observed with erlotinib across clinical subgroups were a better reflection of the merits of the sequential combination regimen. Although the observed difference in PFS did not appear to translate to an OS benefit with sequential erlotinib, the CIs for OS were wide (0.70 to 1.69), and the results were likely confounded by a substantially higher rate of subsequent treatment in the placebo plus chemotherapy arm (78% *v* 51% for erlotinib plus chemotherapy). Furthermore, the study was not powered to detect a difference in OS.

In our study, the sequential combination of chemotherapy and erlotinib stopped at week 24 (6 cycles), and after this time, patients who had not progressed received erlotinib or placebo as maintenance therapy. The separation of the Kaplan-Meier curves for PFS that began during the sequential combination phase of treatment was sustained during weeks 24 to 48, suggesting that maintenance treatment with erlotinib also contributes to the overall PFS benefit observed. The results of recent studies[22-24] support the use of maintenance therapy; in these studies, maintenance chemotherapy improved PFS when compared with no active treatment, but OS data are pending. More recently, it has been reported that in the phase III, placebo-controlled SATURN study, maintenance therapy with erlotinib significantly prolonged PFS in patients who did not progress on first-line chemotherapy.[25] Because of substantial differences in study design and patient population between the SATURN study and this study, a comparison of outcomes between these trials is not possible.

Biomarker data were obtained for only a minority of patients included in the study, so firm conclusions cannot be drawn regarding any association with clinical outcomes. The high incidence of *EGFR* mutations in Asian populations may contribute to the benefit observed with sequential erlotinib in this study. Indeed, two patients with *EGFR* mutations obtained a substantial benefit with sequential erlotinib (PFS, 56 to 82+ weeks), when compared with five patients in the placebo arm who had *EGFR* mutations (PFS, 9 to 25 weeks). However, clinical selection was not performed in this study, and the population included a substantial proportion of patients from subgroups not typically associated with *EGFR* mutations: 70% males, 33% nonadenocarcinoma, and 66% current or former smokers. Probable efficacy in patients with wild-type *EGFR* was evident from the trend toward improved PFS with sequential erlotinib among ever smokers (HR, 0.56). Interestingly, a substantial benefit was observed with sequential erlotinib in one patient with wild-type *EGFR* (PFS, 80+ weeks). Thus, the observed improvement in PFS (HR, 0.47) may be partially attributed to, but not restricted to, patients with *EGFR* mutations.

Table 3. Baseline Demographics and Treatment Outcomes for Patients With Known *EGFR* Mutation Status

Patient	Sex	Histology	Smoking Status	*EGFR* Mutation Status	Study Treatment Received	Best Overall Response	PFS (weeks)
1	M	Adeno	Current	Wild-type	GC-erlotinib	PR*	80†
2	M	Squamous	Former	Wild-type	GC-erlotinib	SD	31
3	M	Nonadeno	Current	Wild-type	GC-erlotinib	SD	26
4	F	Adeno	Current	Wild-type	GC-erlotinib	PD	10
5	F	Adeno	Never	Exon 19 deletion	GC-erlotinib	PR*	82†
6	M	Adeno	Current	Exon 19 deletion	GC-erlotinib	PR*	56
7	M	Adeno	Current	Wild-type	GC-placebo	SD	31
8	M	Nonadeno	Current	Wild-type	GC-placebo	SD	24
9	F	Adeno	Current	Wild-type	GC-placebo	SD	8
10	F	Adeno	Never	Wild-type	GC-placebo	PD	7
11	M	Adeno	Current	Wild-type	GC-placebo	PD	7
12	M	Adeno	Never	Other mutation‡	GC-placebo	PR*	23
13	F	Adeno	Never	Exon 19 deletion	GC-placebo	PR*	25
14	F	Adeno	Current	L858R	GC-placebo	SD	24
15	M	Squamous	Never	L858R	GC-placebo	PR*	25
16	F	Adeno	Never	L858R	GC-placebo	SD	18
17	M	Adeno	Former	L858R	GC-placebo	PD	9

Abbreviations: EGFR, epidermal growth factor receptor; PFS, progression-free survival; Adeno, adenocarcinoma; GC, gemcitabine plus cisplatin or carboplatin; PR, partial response; SD, stable disease; PD, progressive disease.
*All partial responses were observed during the sequential combination phase.
†Patient remained progression-free at the time of the analysis.
‡Exon 20 mutation.

Intermittent dosing of erlotinib with chemotherapy was well tolerated, with no added hematologic toxicity. Dose reductions and dose interruptions were uncommon with erlotinib. Sixty-five percent of patients in the GC-erlotinib arm had skin rash, but only 3% of these patients had grade 3 or higher. This is in contrast with patients who received erlotinib concurrently with chemotherapy in the TRIBUTE study, where the incidence of grade 3 rash was 7.2%.[8] Diarrhea was more common in the GC-erlotinib arm (22% *v* 6% in the GC-placebo arm), but all patients had grade 1 or 2. Despite a previously reported risk of ILD in Asian patients receiving an EGFR TKI, none of the patients in this study developed ILD. The use of intermittent dosing may have contributed to this observation.

Table 4. Incidence and Severity of Commonly Reported Treatment-Related AEs

	GC-Erlotinib Arm (n = 74)				GC-Placebo Arm (n = 79)			
	All Grades		Grade 3+		All Grades		Grade 3+	
Treatment-Related AE	No.	%	No.	%	No.	%	No.	%
Total patients with ≥ 1 AE	70	95	27	36	70	89	28	35
Nonhematologic								
Rash	48	65	2	3	27	34	0	0
Nausea	28	38	2	3	33	42	0	0
Anorexia	25	34	1	1	25	32	1	1
Fatigue	19	26	0	0	13	16	1	1
Alopecia	18	24	1	1	18	23	0	0
Vomiting	17	23	2	3	24	30	5	6
Dry skin	15	20	1	1	6	8	0	0
Pruritus	9	12	0	0	5	6	0	0
Diarrhea	16	22	0	0	5	6	1	1
Malaise	2	3	1	1	6	8	1	1
Pyrexia	4	5	0	0	5	6	2	3
Myalgia	4	5	0	0	5	6	0	0
Stomatitis	7	9	0	0	3	4	0	0
Mucosal inflammation	5	7	0	0	1	1	0	0
Hematologic								
Anemia	17	23	5	7	11	14	5	6
Neutropenia	14	19	10	14	14	18	8	10
Thrombocytopenia	6	8	4	5	7	9	4	5
Biochemical								
ALT increased	3	4	0	0	7	9	2	3

Abbreviations: AE, adverse event; GC, gemcitabine plus cisplatin or carboplatin.

The novel sequential schedule employed in this study was used to avoid the potential issue of cell cycle–based antagonism between EGFR TKIs and chemotherapy. The observed magnitude of improvement is in contrast with outcomes reported for concurrent erlotinib plus chemotherapy (TRIBUTE and TALENT studies); it appears, therefore, that this sequential schedule has been successful in that respect. The optimal sequential schedule of erlotinib with chemotherapy remains to be confirmed. The half-life of erlotinib is approximately 36 hours.[26] In theory, according to the pharmacodynamic separation model,[11] erlotinib should be stopped 2 to 3 days before gemcitabine infusion in subsequent cycles, but the impact of such a schedule is currently unknown. In another randomized phase II study, a 7-day EGFR TKI–free period was scheduled before each subsequent cycle of carboplatin/paclitaxel chemotherapy in patients with chemotherapy-naïve NSCLC that expressed EGFR or had a high *EGFR* gene copy number.[27] A tumor response rate of 24% and PFS of 4.6 months were reported for the sequential combination arm. The schedule employed in this study achieved a greater response rate and longer PFS than those observed with the alternative schedule.

The standard 4-week schedule of gemcitabine includes doses of 1,000 mg/m^2 on days 1, 8, and 15. The day 15 dose could not be administered in this study because of sequential erlotinib on days 15 to 28; however, the doses on days 1 and 8 were increased to 1,250 mg/m^2. Patients in the GC-placebo arm attained a response rate of 24.4% and PFS of 23.4 weeks, which is similar to treatment outcomes observed

with gemcitabine/platinum therapy in other randomized studies.[28,29] In this study, the cytotoxic regimen of both treatment arms was the same, and the arms were well balanced. Therefore, the improvements in response rate and PFS are likely to be due to the sequential combination of chemotherapy with erlotinib, followed by erlotinib maintenance therapy.

In conclusion, first-line sequential administration of erlotinib with chemotherapy has demonstrated promising results in patients with advanced NSCLC. This treatment strategy warrants further investigation in a phase III study.

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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REFERENCES

1. Ramalingam S, Belani C: Systemic chemotherapy for advanced non-small cell lung cancer: Recent advances and future directions. Oncologist 13:5-13, 2008 (suppl 1)
2. Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 26:3543-3551, 2008
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. Bezjak A, Tu D, Seymour L, et al: Symptom improvement in lung cancer patients treated with erlotinib: Quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 24:3831-3837, 2006
5. Groen H, Arrieta OG, Riska H, et al: The global TRUST study of erlotinib in advanced non-small-cell lung cancer (NSCLC). J Clin Oncol 26:706s, 2008 (suppl; abstr 19000)
6. Giaccone G, Herbst RS, Manegold C, et al: Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: A phase III trial–INTACT 1. J Clin Oncol 22:777-784, 2004
7. Herbst RS, Giaccone G, Schiller JH, et al: Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: A phase III trial–INTACT 2. J Clin Oncol 22:785-794, 2004
8. 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
9. Gatzemeier U, Pluzanska A, Szczesna A, et al: Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva Lung Cancer Investigation Trial. J Clin Oncol 25:1545-1552, 2007
10. Piperdi B, Ling Y, Kroog G, et al: Schedule-dependent interaction between epidermal growth factor inhibitors (EGFRI) and G2/M blocking chemotherapeutic agents (G2/MB) on human NSCLC cell lines in vitro. J Clin Oncol 23:620, 2004 (suppl; abstr 7028)
11. 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
12. Li T, Ling YH, Goldman ID, et al: Schedule-dependent cytotoxic synergism of pemetrexed and erlotinib in human non-small cell lung cancer cells. Clin Cancer Res 13:3413-3422, 2007
13. Solit DB, She Y, Lobo J, et al: Pulsatile administration of the epidermal growth factor receptor inhibitor gefitinib is significantly more effective than continuous dosing for sensitizing tumors to paclitaxel. Clin Cancer Res 11:1983-1989, 2005
14. Mahaffey CM, Davies AM, Lara PN Jr, et al: Schedule-dependent apoptosis in K-ras mutant non-small-cell lung cancer cell lines treated with docetaxel and erlotinib: Rationale for pharmacodynamic separation. Clin Lung Cancer 8:548-553, 2007
15. Davies AM, Hesketh PJ, Beckett L, et al: Pharmacodynamic separation of erlotinib and docetaxel (DOC) in advanced non-small cell lung cancer (NSCLC): Overcoming hypothesized antagonism. J Clin Oncol 25:413s, 2007 (suppl; abstr 7618)
16. Davies AM, Ho C, Beckett L, et al: Intermittent erlotinib (ERL) in combination with pemetrexed (PEM): Phase I schedules designed to achieve pharmacodynamic separation. J Clin Oncol 26:1431s, 2008 (suppl; abstr 8032)
17. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization 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
18. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. Biometrics 31:103-115, 1975
19. Schneider CP, Heigener D, Schott-von-Römer K, et al: Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer. An analysis of patients from German centers in the TRUST study. J Thoracic Oncol 3:1446-1453, 2008
20. 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
21. Lara PN Jr, Redman MW, Kelly K, et al: Disease control rate at 8 weeks predicts clinical benefit in advanced non-small-cell lung cancer: Results from Southwest Oncology Group randomized trials. J Clin Oncol 26:463-467, 2008
22. Fidias P, Dakhil S, Lyss A, et al: Phase III study of immediate versus delayed docetaxel after induction therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer: Updated report with survival. J Clin Oncol 25:388s, 2007 (suppl; abstr LBA7516)
23. Ciuleanu TE, Brodowicz T, Belani CP, et al: Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III study. J Clin Oncol 26:426s, 2008 (suppl; abstr 8011)
24. Soon Y, Stockler MR, Boyer M, et al: Duration of chemotherapy for advanced non-small cell

lung cancer: An updated systematic review and meta-analysis. J Clin Oncol 26:1427s 2008 (suppl; abstr 8013)

25. Roche press release. http://www.roche.com/media/media_releases/med-cor-2008-11-07.htm

26. Lu JF, Eppler SM, Wolf J, et al: Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure–safety relationship in patients with non-small cell lung cancer. Clin Pharmacol Ther 80:136-145, 2006

27. Camidge DR, Kabbinavar F, Martins R, et al: EGFR biomarker-selected randomized phase II study of erlotinib (E) or intercalated E with carboplatin/paclitaxel (C/P) in chemo-naïve advanced NSCLC. J Thorac Oncol 3:S268, 2008 (suppl 4; abstr 14)

28. 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

29. 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

