A Randomized Phase II Trial of First-Line Treatment with Gemcitabine, Erlotinib, or Gemcitabine and Erlotinib in Elderly Patients (Age ≥70 Years) with Stage IIIB/IV Non-small Cell Lung Cancer

Thomas E. Stinchcombe, MD, Amy H. Peterman, PhD,† Carrie B. Lee, MD, MPH,* Dominic T. Moore, MPH,‡ Jennifer L. Beaumont, MS,§ Daniel S. Bradford, MD,‖ Kamal Bakri, MD,¶ Mark Taylor, MD,# Jeffrey M. Crane, MD,** Garry Schwartz, MD,†† Thomas A. Hensing, MD,‡‡ Edwin McElroy, Jr., MD,§§ Harvey B. Niell, MD,‖‖ Harry D. Harper, MD,¶¶ Sridhar Pal, MD,## and Mark A. Socinski, MD**

Introduction: Single-agent gemcitabine is a standard of care for elderly patients with advanced non-small cell lung cancer, but novel therapies are needed for this patient population.

Methods: We performed a noncomparative randomized phase II trial of gemcitabine, erlotinib, or the combination in elderly patients (age ≥70 years) with stage IIIB or IV non-small cell lung cancer. Patients were randomized to arms: A (gemcitabine 1200 mg/m^2 on days 1 and 8 every 21 days), B (erlotinib 150 mg daily), or C (gemcitabine 1000 mg/m^2 on days 1 and 8 every 21 days and erlotinib 100 mg daily). Arms B and C were considered investigational; the primary objective was 6-month progression-free survival.

Results: Between March 2006 and May 2010, 146 eligible patients received protocol therapy. The majority of the patients (82%) had stage IV disease, 64% reported adenocarcinoma histology, 90% reported current or previous tobacco use, and 28% had a performance status of 2. The 6-month progression-free survival rate observed in arms A, B, and C was 22% (95% confidence interval [CI] 11–35), 24% (95% CI 13–36), and 25% (95% CI 15–38), respectively; the median overall survival observed was 6.8 months (95% CI 4.8–8.5), 5.8 months (95% CI 3.0–8.3), and 5.6 months (95% CI 3.5–8.4), respectively. The rate of grade ≥3 hematological and nonhematological toxicity observed was similar in all three arms. The best overall health-related quality of life response did not differ between treatment arms.

Conclusions: Erlotinib or erlotinib and gemcitabine do not warrant further investigation in an unselected elderly patient population.

Key Words: Quality of life, Cumulative illness rating scale for geriatrics, Targeted therapy, Elderly.

(*J Thorac Oncol.* 2011;6: 1569–1577)

Lung cancer remains the leading cause of cancer mortality in the United States and the world, with approximately 85% of cases non-small cell lung cancer (NSCLC).[1–3] The majority of patients with NSCLC have advanced disease at the time of diagnosis, and the goals of treatment are to extend survival, improve health-related quality of life (HRQL), and reduce disease-related symptoms.[4,5] Many elderly patients with advanced NSCLC have significant cardiovascular and pulmonary comorbidities related to tobacco exposure and comorbidities associated with advanced age, which impacts their ability to tolerate the treatment of NSCLC. According to the Surveillance, Epidemiology, and End Results registry, the median age at the time of diagnosis of lung cancer in the United States is 69 years.[6] The definition of "elderly" has

*Division of Hematology/Oncology, Multidisciplinary Thoracic Oncology Program, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; †Department of Psychology, University of North Carolina at Charlotte, Charlotte, North Carolina; ‡Division of Biostatistics and Data Management, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; §Department of Medical Social Sciences, Feinberg School of Medicine at Northwestern University, Chicago, Illinois; ‖Highlands Oncology Group, Fayetteville, Arkansas; ¶Cape Fear Valley Health System Cancer Center, Fayetteville, North Carolina; #Savannah Hematology and Oncology, Savannah, Georgia; **Rex Hematology and Oncology, Raleigh, North Carolina; ††Carolinas Medical Center Northeast, Concord, North Carolina; ‡‡North Shore University Health System, Evanston, Illinois; §§Wellmont-Kingsport Hematology and Oncology Associates, Kingsport, Tennessee; ‖‖Memphis Veterans Affairs Medical Center, Memphis, Tennessee; ¶¶Northern New Jersey Cancer Associates, Hackensack, New Jersey; and ##Carolinas Hematology and Oncology Associates, Charlotte, North Carolina.

Disclosure: Dr. Socinski reports that his institution received research funding from Genentech. Dr. Stinchcombe reports being on the Genentech speakers bureau in 2009, and his institution received research funding for clinical trials in 2010 and 2011. Ms. Beaumont reports that her employing organization received a grant for research funding to develop patient reported symptom indices for advanced cancer, including lung cancer. The other authors have no financial disclosures.

Address for correspondence: Thomas E. Stinchcombe, MD, Lineberger Comprehensive Cancer Center at the University of North Carolina, 170 Manning Drive, Physicians Office Building, 3rd Floor, Cb 7305, Chapel Hill, NC 27599-7. E-mail: Thomas_Stinchcombe@med.unc.edu

Presented as a poster at the 2010 Annual American Society of Clinical Oncology meeting, June 4–8, Chicago, lllinois.

ISSN: 1556-0864/11/0609-1569

varied among oncology trials, but for trials of advanced NSCLC, the age ≥70 years is frequently used.[7] The number of elderly patients with advanced NSCLC is expected to increase as the size elderly population continues to increase in the next several decades.[8]

Elderly specific trials compared with age-unspecified trials recruit a more elderly population; among elderly patients in elderly specific trials compared with age-unspecified trials, a lower rate of grade ≥3 toxicities is observed.[9] Several elderly specific phase III trials in advanced NSCLC had been performed when this trial was designed. Single-agent vinorelbine was compared with best supportive care ($n = 161$), and patients assigned to the vinorelbine arm experienced longer survival, improvement in quality of life (Qol) functioning scales, and fewer lung cancer-related symptoms.[10] A subsequent phase III trial ($n = 698$) compared single-agent vinorelbine or gemcitabine with the combination of gemcitabine and vinorelbine; the combination was not more effective than single-agent vinorelbine or gemcitabine.[11] The Qol was similar in all three treatment arms but a higher rate of toxicity was observed in the combination arm. A smaller phase III trial ($n = 120$) compared vinorelbine with the combination of gemcitabine and vinorelbine; the combination was associated with superior survival and a delay in symptom and Qol deterioration.[12] When this trial was designed, single-agent vinorelbine or gemcitabine were considered standard therapies for elderly patients with advanced NSCLC.

A single-arm phase II trial of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), in elderly patients with advanced NSCLC had revealed promising survival and a low rate of toxicity.[13] A single-arm phase II trial of docetaxel and gefitinib in elderly patients with advanced NSCLC revealed acceptable toxicity and promising efficacy.[14] The combination of gemcitabine and erlotinib compared with single-agent gemcitabine had revealed superior survival in patients with advanced pancreatic cancer;[15] of the patients enrolled in the gemcitabine and erlotinib arm, 80% received an erlotinib dose of 100 mg daily. Data reporting the efficacy and toxicity of gemcitabine and erlotinib in advanced NSCLC were not available when this trial was designed and the role of EGFR mutations in the selection of patients for EGFR TKI therapy was not known when this trial was designed. We designed a randomized phase II trial to investigate the activity of erlotinib alone and in combination with gemcitabine in elderly patients with advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have a histologic or cytologic diagnosis of stage IIIB or IV NSCLC (all histologies), aged ≥70 years, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2. Patients could not have received treatment for metastatic NSCLC; patients could have received prior adjuvant chemotherapy, but time since prior adjuvant chemotherapy was required to be ≥1 year. Patients were required to have adequate hematological function (defined as absolute neutrophil count [ANC] ≥1500/mm^3, platelets count ≥100,000/mm^3, hemoglobin ≥8.0 g/dl), hepatic function (defined as aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 × upper limit of normal [ULN], alkaline phosphatase [AP] ≤4 × ULN, and total bilirubin ≤ULN), and renal function (defined as serum creatinine ≤1.5 × ULN). Patients were required to have evaluable disease by RECIST.[16] Patients with asymptomatic treated brain metastases were eligible. Patients with a history of severe hypersensitivity reactions to gemcitabine, incompletely healed from previous oncologic or major surgery, unable to participate in the HRQL questionnaires or provide informed consent were ineligible. This trial was reviewed and approved by the institutional review board of all the participating centers, and patients were required to provide informed consent before any study related tests were performed. The study was registered with ClinicalTrials.gov (NCT00283244).

Treatment

Patients assigned to arm A received gemcitabine 1200 mg/m^2 intravenously on days 1 and 8 every 21 days until disease progression, unacceptable toxicity, or a maximum of four cycles. At the time of disease progression, patients were offered erlotinib 150 mg orally daily until disease progression or unacceptable toxicity. Patients assigned to arm B received erlotinib 150 mg orally daily until disease progression or unacceptable toxicity, and patients assigned to arm C received gemcitabine 1000 mg/m^2 intravenously on days 1 and 8 every 21 days in combination erlotinib 100 mg daily. In arm C, patients received gemcitabine until disease progression, unacceptable toxicity, or for a maximum of four cycles; after four cycles of gemcitabine, patients continued single-agent erlotinib until disease progression or unacceptable toxicity. Patients in arm C could undergo dose escalation of erlotinib to 150 mg daily in cycle 2 at the discretion of the treating physician if no grade ≥2 or higher toxicity typical of erlotinib was observed during the first cycle. In all three treatment arms, 21 days was considered one cycle.

For patients who experienced grade 3 rash or diarrhea related to erlotinib, treatment was interrupted until toxicity resolved to grade ≤1 and then resumed erlotinib with a 50 mg dose reduction. For the second episode of grade 3, rash or diarrhea the erlotinib dose was reduced to 50 mg in arm B and 25 mg in arm C. Patients discontinued study treatment if they developed grade 4 rash, diarrhea, or possible interstitial lung disease.

Patients were required to have an ANC ≥1500/mm^3 and a platelet count ≥100,000/mm^3 before the next cycle; if the ANC or platelets were below the threshold, they were checked weekly. If ANC and platelets were not within acceptable limits after more than 2-week delay, the patient discontinued study treatment. If a patient experienced febrile neutropenia, an ANC less than 500/mm^3 for ≥5 days, or platelet count less than 50,000/mm^3, the gemcitabine dose in arm A was reduced from 1200 mg/mm^3 to 900 mg/m^2: in arm C, the gemcitabine dose was reduced from 1000 to 800 mg/m^2. For day 8 gemcitabine treatment, patients were required to have an ANC ≥1000/mm^3 and a platelet count more than 75,000/mm^3 to receive the full dose of gemcitabine; patients with ANC of 500 to 999/

mm^3 or platelet count 50 to 74,000/mm^3 received 75% of the day 1 gemcitabine dose. The day 8 gemcitabine was omitted for patients with ANC less than 500/mm^3 or platelet count less than 50,000/mm^3.

Study Assessments

Patients were required to have a staging computed tomography scan of the chest and abdomen (including the liver and adrenals) within 4 weeks of trial enrollment. Bone scan, positron emission tomography, and computed tomography or magnetic resonance imaging of the brain were not required and were performed if clinically indicated. Patients underwent laboratory assessment with a complete blood count (CBC), AST, ALT, AP, and creatinine; assessment of Eastern Cooperative Oncology Group PS; and physical examination at baseline visit. Patients were assessed using the Cumulative Illness Rating Scale for Geriatrics at baseline (Figure 1).[17] Patients had tumor specimens and blood samples collected for a correlative science studies, which will be reported separately.

Before each treatment cycle; patients underwent a laboratory examination (CBC, AST, ALT, AP, and creatinine), physical examination, and toxicity assessment using the Common Toxicity Criteria for Adverse Events version 3.0 (National Cancer Institute, Bethesda, MD). Patients in the gemcitabine containing arms had a CBC assessed weekly for hematological toxicity. Response was assessed according to RECIST after cycles 2 and 4 and then at 6 months from start of treatment or if clinically indicated; after 6 months, response was assessed every 2 months.

PATIENT _____ AGE _____

RATER _____ DATE _____

Instructions: Please refer to the CIRS-G manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use reverse side for more writing space).

RATING STRATEGY 0- No problem
1- Current mild problem or past significant problem
2- Moderate disability or morbidity/requires "first line" therapy
3- Severe/constant significant disability/"uncontrollable" chronic problems
4- Extremely severe/immediate treatment required/end organ failure/severe impairment in function

		SCORE
1	HEART	
2	VASCULAR	
3	HAEMATOPOIETIC	
4	RESPIRATORY	
5	EYES, EARS, NOSE, THROAT AND LARYNX	
6	UPPER GI	
7	LOWER GI	
8	LIVER	
9	RENAL	
10	GENITOURINARY	
11	MUSCULOSKELETAL/INTEGUMENT	
12	NEUROLOGICAL	
13	ENDOCRINE/METABOLIC AND BREAST	
14	PSYCHIATRIC ILLNESS	
	TOTAL NUMBER OF CATEGORIES ENDORSED	
	TOTAL SCORE	
	Severity index: (total score/total number of categories endorsed)	
	Number of categories at level 3 severity	
	Number of categories at level 4 severity	

FIGURE 1. Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[17]

HRQL and Symptom Assessment

Participants' HRQL was evaluated using the functional assessment of cancer therapy for lung cancer (FACT-L),[18,19] which consists of the FACT-General and the lung cancer-specific subscale (LCS). The FACT-General is a measure of general Qol and contains the subscales of physical well-being, social/family well-being, emotional well-being, and functional well-being (FWB). The Trial Outcome Index-Lung (TOI-L) consists of the physical well-being, FWB, and LCS subscales. The TOI-L was the primary HRQL indicator analyzed, with the total FACT-L and LCS used as secondary indicators.

The FACT-L was administered at the screening visit (within 2 weeks of day 1 of the first treatment cycle) or on day 1, after each cycle (3 weeks), after completion of treatment, or at the time the patient was withdrawn from the study. Patients completed the questionnaire in private before the doctor's visit or any investigations or discussions with the patient about his or her disease status or treatment.

Statistical Methods and Study Design

Efficacy Analysis

The objective of this randomized phase II trial was to test if one or both of the investigational arms (B and C) would be worthy of further investigation; arm A was used as an "internal control" arm to ascertain if the progression-free survival (PFS) rate in this cohort of patients differs substantially from that of the previous trial of single-agent gemcitabine.[11] The randomized phase II design was not meant to be comparative between the treatment arms. The primary endpoint was 6-month PFS, and the 6-month PFS observed with single-agent gemcitabine in a previous phase III trial was 29%.[11] If a 6-month PFS of 45% was observed in arms B and C, then the treatment would be considered worthy of further investigation. With an α error of 10%, 49 patients per arm (a total of 147) provided an 85% power to reject the null hypothesis of 6-month PFS of 29%. Patients were stratified based on gender, smoking status (never [never defined as $<$100 cigarettes in a lifetime] or light [$\leq$10 pack-years and quit $\geq$15 year ago] versus current or former smoker and PS (0 or 1 versus 2) using a constrained block randomization. PFS was defined as time between enrollment and disease progression or death, which ever event occurred first, with censoring for patients alive without progression at last contact. Overall survival (OS) was defined as time between enrollment and death or last contact. Estimates of median PFS and OS and 6-month PFS were calculated using the Kaplan-Meier method.[20]

Statistical analyses related to efficacy were performed using both SAS and R statistical software. SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC) was used. R is an open source statistical programming language from the R Development Core Team (2008; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0; http://www.R-project.org).

HRQL Analysis

The completeness of the HRQL data was described by calculating the number of forms completed by each subject

divided by the number of forms expected. A questionnaire was considered completed if enough questions were answered to obtain a valid total score. Analyses focused on the assessments at baseline (cycle 1 day 1 if available, otherwise used pretreatment screening data), cycle 2, cycle 3, cycle 4, and at end of treatment (EOT). Before conducting the primary analyses, patterns of missing data across these time points were summarized. Patients were classified as "completers" if they completed an EOT assessment and as "noncompleters" otherwise. Baseline TOI, FACT-L, and LCS scores were compared between completers and noncompleters. A χ^2 test was also conducted to evaluate whether the proportion of completers differed between study arms. All HRQL analyses were performed using SAS version 9.2 (SAS Institute Inc.).

HRQL treatment response scores were calculated based on absolute change from baseline to each subsequent assessment point and were classified as improved, worsened, or no change based on previously reported estimates of clinically significant change.[21] On the TOI-L and FACT-L, a change of 6 points or more indicated change. For the LCS, a change of 2 or more points indicated change. The best overall HRQL response to treatment was then determined as follows. Two visits with a response of "improved" without an interim visit response of worsened was required to be classified as an improvement. A best response of "no change" was assigned to subjects who did not qualify for "improved" but who had two visit responses of "improved" or "no change" with no interim visit where HRQL "worsened." A best overall response of "worsened" was assigned for those subjects who had two consecutive visit responses of "worsened." Subjects who did not meet any of these criteria were assigned an overall treatment response of "other."

Finally, we calculated the percentage of subjects in each treatment arm who fell into each overall treatment response category. A score improvement rate was calculated as the percentage of patients with best overall score response of "improved." A score control rate was calculated as the percentage of patients with a best overall score response of either "improved" or "no change." A score worsened rate was calculated as the percentage of patients with a best overall score response of "worsened."

No expected HRQL increase was specified a priori. Instead, χ^2 statistics were used to compare visit responses between treatment arms at each assessment and overall rate of improvement, worsening, or no change. We also used a mixed effects model for repeated measures to evaluate the TOI-L, FACT-L Total, and LCS scores longitudinally. Mixed effects models describe the rate of change in HRQL scores over time for each treatment arm (fixed effect), taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change (random effect) into the model. Mixed effects models use all available data and do not discard subjects from the overall analysis when individual assessments are missing.

RESULTS

Patients

Between March 2006 and May 2010, 160 patients were enrolled on the trial (Figure 2); 13 patients did not initiate study treatment because of the following reasons: withdrew informed consent ($n = 5$), referred to hospice ($n = 4$), ineligible ($n = 3$), and death before treatment ($n = 1$). One patient received treatment on trial and was subsequently found to be ineligible because of an incorrect diagnosis. The characteristics of the patients enrolled and treated on the trial are presented in Table 1. The median age in treatment arms A, B, and C was 74, 76, and 78 years, respectively. The majority of the patients had stage IV disease (82%), and adenocarcinoma histology (64%). Of the patients with a known smoking history, approximately 90% of patients were current smokers or had a history of smoking, and 28% of patients had a PS of 2. The median Cumulative Illness Rating Scale for Geriatrics score in arms A, B, and C was 11.5, 10, and 11, respectively.

Treatment Administration and Toxicity

The median number of cycles in treatment arms A, B, and C was 4 (range 1–4), 2 (range 1–39), and 4 (range 1–9), respectively. The most common reasons for treatment discontinuation were adverse events and disease progression (Figure 2). Of the 44 patients in arm A, 19 received erlotinib at the time of disease progression; in arms B ($n = 51$) and C ($n =$

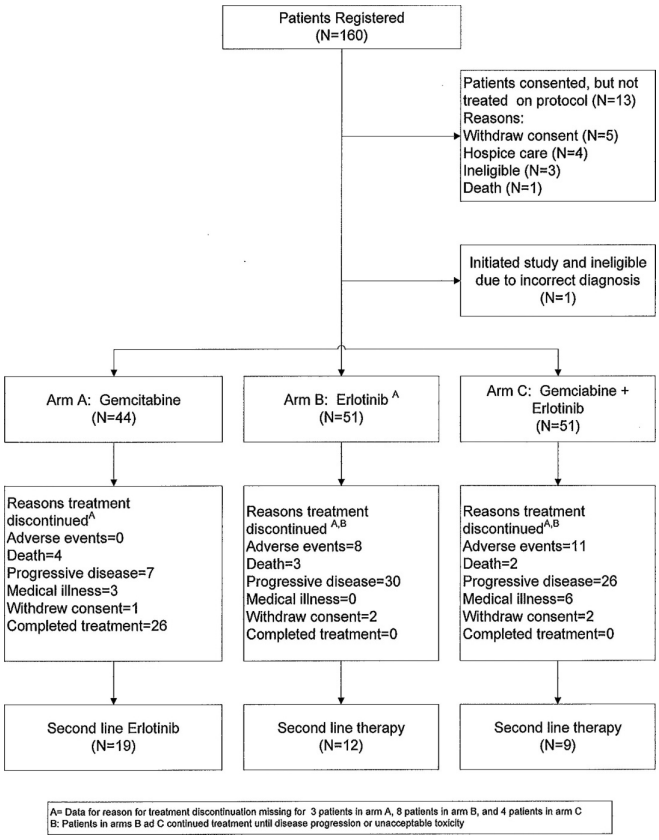

FIGURE 2. Trial schema and patient flow diagram.

TABLE 1. Patient Characteristics

Characteristic	Gemcitabine	Erlotinib	Gemcitabine/ Erlotinib
n	44	51	51
Median age, yr (range)	74 (70–86)	76 (69–86)	78 (70–90)
Stage, *n* (%)			
IIIB	11 (25)	5 (10)	10 (20)
IV	33 (75)	46 (90)	41 (80)
Gender, *n* (%)			
Male	22 (50)	24 (47)	27 (53)
Female	22 (50)	27 (53)	24 (47)
Performance status, *n* (%)			
0	10 (23)	7 (14)	6 (12)
1	21 (48)	29 (57)	29 (57)
2	13 (29)	14 (27)	14 (27)
Missing	0 (0)	1 (2)	2 (4)
Smoking history, *n* (%)			
Never or light	4 (9)	6 (12)	5 (10)
Current or former	35 (80)	43 (84)	42 (82)
Missing	5 (11)	2 (4)	4 (8)
Histology, *n* (%)			
Adenocarcinoma	28 (64)	34 (67)	31 (61)
Squamous	7 (16)	5 (10)	8 (16)
Not otherwise specified	8 (18)	12 (23)	12 (24)
Large cell carcinoma	1 (2)	0 (0)	0 (0)
CIRS-G frailty scale[a]			
Median total score (range)	11.5 (0–25)	10 (2–24)	11 (4–24)
Median severity index	0.8	0.7	0.8
No. of categories at level 3	3	0	2
No. of categories at level 4	0	1	0

[a] Data missing on one patient.
CIRS-G, Cumulative Illness Rating Scale for Geriatrics.

TABLE 2. Grade ≥3 Hematologic Toxicities

Toxicity	Arm A (Gemcitabine)	Arm B (Erlotinib)	Arm C (Gemcitabine + Erlotinib)
Anemia	1 (2)	0 (0)	4 (8)
Neutropenia	4 (9)	1 (2)	1 (2)
Thrombocytopenia	3 (7)	1 (2)	2 (4)
Febrile neutropenia	0 (0)	0 (0)	0 (0)

Data are presented as *n* (%).

51), 12 and 9 patients, respectively, received further therapy at the time of disease progression therapy. The rate of grade ≥3 hematological toxicities observed in arms A, B, and C are presented in Table 2; the rate of grade ≥3 neutropenia was low in all three arms, and no episodes of febrile neutropenia were observed. The rate of grade ≥3 treatment-related nonhematological toxicities occurring in ≥5% of patients is presented in Table 3. The rate of grade ≥3 nonhematological toxicities was ≤10% in all 3 treatment arms. Two grade 5 toxicities (pneumonitis and renal failure) were observed in arm C; no grade 5 toxicities were observed in the other treatment arms. The rate of acne/acneiform rash (all grades) observed in arms A, B, and C was 20, 45, and 47%, respectively.

TABLE 3. Common (≥5% in Any Arm) Grade ≥3 Nonhematologic Toxicities

Toxicity	Arm A (Gemcitabine)	Arm B (Erlotinib)	Arm C (Gemcitabine + Erlotinib)
Dehydration	0 (0)	3 (6)	2 (4)
Diarrhea	0 (0)	3 (6)	3 (6)
Dyspnea	2 (5)	0 (0)	3 (6)
Fatigue	4 (9)	1 (2)	5 (10)
Rash	1 (2)	2 (4)	3 (6)

Data are presented as *n* (%).

TABLE 4. Efficacy Results

	Gemcitabine	Erlotinib	Gemcitabine + Erlotinib
Overall response rate, %	7	0	21
Median PFS (95% CI), mo	3.7 (2.3–4.7)	2.8 (1.4–3.4)	4.1 (2.4–5.0)
6 Month PFS rate (95% CI), %	22 (11–35)	24 (13–36)	25 (15–38)
Median OS (95% CI), mo	6.8 (4.8–8.5)	5.8 (3.0–8.3)	5.6 (3.5–8.4)

CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Efficacy Results

The median follow-up for survivors is 12.3 months (range 3.5–39 months). Of the 146 patients treated in the trial, 140 have experienced disease progression or death. The 6-month PFS observed in arms A, B, and C was 22% (95% confidence interval [CI] 11–35), 24% (95% CI 13–36), and 25% (95% CI 15–38), respectively; the median PFS was 3.7 (95% CI 2.3–4.7), 2.8 (95% CI 1.4–3.4), and 4.1 (95% CI 2.4–5.0) months, respectively (Table 4 and Figure 3). Of the 146 patients treated in the trial, 130 have died. The median OS observed in arms A, B, and C was 6.8 (95% CI 4.8–8.5), 5.8 (95% CI 3.0–8.3), and 5.6 (95% CI 3.5–8.4) months, respectively (Table 4 and Figure 4). The overall response rate observed in arms A, B, and C was 7, 0, and 21%, respectively. Of the 45 patients who received treatment in arm A, 19 patients received second-line erlotinib, and 18 patients have experienced disease progression or death. The response rate and median PFS observed with second-line erlotinib was 11% (95% CI 1–33; 2 patients) and 1.6 months (95% CI 0.9–3.7 months), respectively. Second-line therapy in treatment arms B and C was at the discretion of the investigator, and data are not available on the agent used or the efficacy observed.

HRQL Analysis

Baseline TOI, FACT-L, and LCS scores did not differ between completers and noncompleters ($p > 0.58$). A χ^2 test was also conducted to evaluate whether the proportion of completers differed between study arms: it did not ($p =$

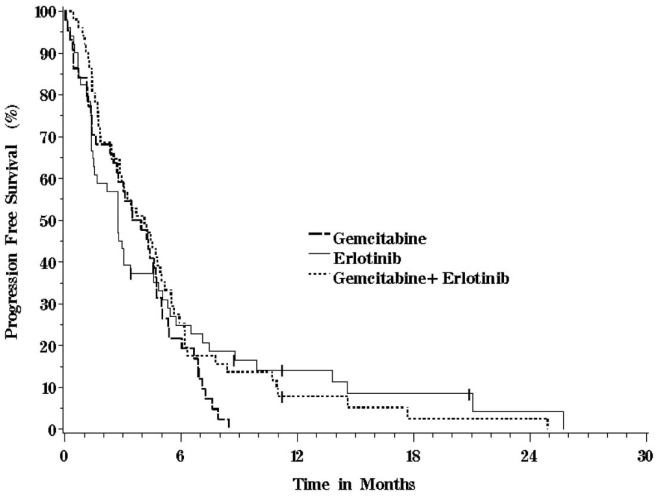

FIGURE 3. Progression-free survival by treatment arm.

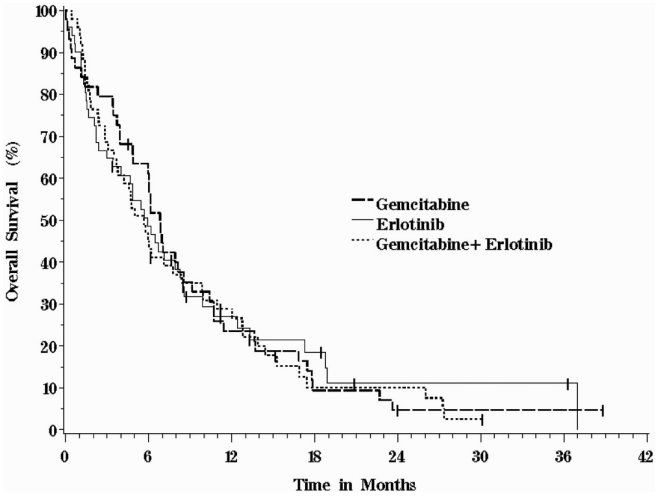

FIGURE 4. Overall survival by treatment arm.

0.877). Of the completers, 32% were in arm A, 34% were in arm B, and 34% were in arm C.

Best Response-to-Treatment Analysis

The best overall HRQL response did not differ between treatment arms on the TOI-L ($p = 0.76$), the LCS ($p = 0.85$), or the FACT-L total score ($p = 0.57$). These results are summarized in Table 5. Because a large number of subjects in each arm were coded as "other" (i.e., they did not meet criteria for better, no change, or worse), we also examined whether the response at each assessment time differed across treatment arms. No significant differences were found in the percent improved, worsened, or with no change at any of the individual assessments ($p > 0.11$).

Longitudinal HRQL Analysis

Table 6 contains descriptive statistics for the HRQL raw scores at each assessment time. Baseline HRQL did not differ between treatment arms ($p > 0.48$). Both the TOI-L and the total FACT-L showed a very slight general downward trend across assessment times that was equivalent between treatment arms, as indicated by a significant effect for time ($p \leq 0.01$ for both) and a nonsignificant time × treatment interaction ($p > 0.95$) in the mixed model. Although the overall time × treatment interaction effect was not significant for the LCS either ($p = 0.62$), the post hoc comparisons indicated that lung cancer symptoms were significantly better in the combined treatment arm than in the gemcitabine only

TABLE 5. Best Response-to-Treatment Analysis

	Gemcitabine ($n = 44$)	Erlotinib ($n = 51$)	Gemcitabine + Erlotinib ($n = 51$)
TOI-L			
Improved	5 (11.4)	6 (11.8)	7 (13.7)
No change	12 (27.3)	9 (17.6)	9 (17.6)
Worsened	11 (25.0)	12 (23.5)	9 (17.6)
Other	16 (36.4)	24 (47.1)	26 (51.0)
LCS			
Improved	7 (15.9)	13 (25.5)	14 (27.4)
No change	7 (15.9)	8 (15.7)	4 (7.8)
Worsened	9 (20.4)	8 (15.7)	6 (11.8)
Other	21 (47.7)	22 (43.1)	27 (52.9)
FACT-L total			
Improved	8 (18.2)	9 (17.6)	8 (15.7)
No change	9 (20.4)	6 (11.8)	7 (13.7)
Worsened	8 (18.2)	7 (13.7)	8 (15.7)
Other	19 (43.2)	29 (56.9)	28 (54.9)

Data are presented as *n* (%).

TOI-L, trial outcome index-lung; LCS, lung cancer symptoms; FACT-L, functional assessment of cancer therapy for lung cancer.

TABLE 6. Longitudinal Health-Related Quality of Life Scores

	Gemcitabine Only	Erlotinib Only	Gemcitabine + Erlotinib
TOI-L			
Baseline	52.8 (14.5), 42	50.5 (14.1), 51	54.0 (14.9), 46
Cycle 2	49.6 (10.3), 31	47.8 (15.1), 36	51.9 (16.0), 35
Cycle 3	50.9 (13.3), 27	51.3 (12.8), 22	52.0 (14.0), 25
Cycle 4	52.2 (13.4), 24	50.2 (17.1), 21	56.5 (12.7), 20
End of treatment	46.5 (14.3), 21	44.5 (18.1), 24	48.8 (14.6), 23
FACT-L total			
Baseline	93.4 (18.9), 42	91.5 (18.4), 50	95.1 (19.5), 45
Cycle 2	91.3 (14.5), 29	90.0 (17.3), 34	94.0 (21.7), 34
Cycle 3	93.5 (18.9), 26	94.3 (16.4), 21	92.3 (20.3), 24
Cycle 4	95.6 (18.0), 24	91.3 (22.0), 20	99.7 (17.5), 19
End of treatment	84.7 (20.4), 21	83.2 (22.3), 22	90.3 (19.9), 22
LCS			
Baseline	16.1 (5.6), 42	15.8 (5.0), 51	17.0 (4.6), 46
Cycle 2	16.1 (3.8), 31	16.2 (5.1), 36	17.4 (5.4), 35
Cycle 3	14.9 (5.2), 27	16.5 (4.5), 23	18.7 (6.0), 25
Cycle 4	16.4 (5.2), 25	15.8 (6.3), 21	19.9 (4.6), 20
End of treatment	14.4 (5.9), 22	15.4 (6.0), 24	17.1 (6.0), 24

Data are presented as mean (SD), *n*.

TOI-L, trial outcome index-lung; LCS, lung cancer symptoms; FACT-L, functional assessment of cancer therapy for lung cancer.

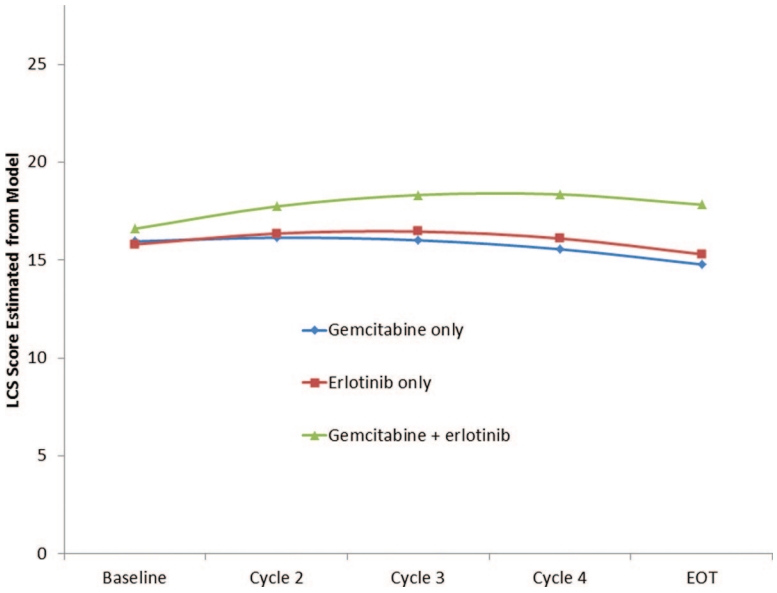

FIGURE 5. Lung Cancer-Specific Subscale Score by Cycle.

arm at the third ($p = 0.04$) and fourth ($p = 0.02$) cycles and at the EOT ($p = 0.04$; Figure 5).

DISCUSSION

The 6-month PFS observed in the erlotinib alone arm did not meet the threshold for further study. When this trial was designed, the predictive role of EGFR mutation in the use of first-line EGFR TKI therapy was not known. Phase III trials compared EGFR TKI's with platinum-based double agent chemotherapy support the use of first-line EGFR TKI therapy in patients whose tumors demonstrated an EGFR mutations.[22–24] Of patients with a known smoking history, approximately 90% enrolled in our study were consider current or former smokers, which is a patient population associated with a lower rate of EGFR mutations. The response rate and PFS results of single-agent erlotinib observed in our trial are similar to first-line gefitinib among patients with EGFR wild-type tumors in the Iressa Pan-Asia Study.[22,25] The rate of rash in the erlotinib alone and erlotinib and gemcitabine arms are numerically lower than trials of maintenance erlotinib and the combination erlotinib and gemcitabine in pancreatic cancer.[15,26] The reasons for this lower rate of rash are unclear.

The Iressa in NSCLC versus Vinorelbine Investigation in The Elderly (INVITE) compared gefitinib with vinorelbine in unselected elderly patients (age ≥70 years); the primary endpoint was PFS.[27] Patients assigned to gefitinib ($n = 97$) compared with vinorelbine ($n = 99$) experienced a similar PFS and OS. The 6-month PFS rate observed in the gefitinib and vinorelbine arms was 14.9 and 23.6%, respectively; the overall response rate observed was 3.1 and 5.1%, respectively. Given the randomized phase II design of our trial and the INVITE trial by Crino et al., definitive conclusions cannot be determined. However, the data from these two trials suggest that treatment with first-line EGFR TKI therapy in an unselected elderly patient population is unlikely to yield significant improvements in efficacy compared with single-agent chemotherapy.

HRQL and symptom control are important assessments when evaluating novel palliative therapies in advanced NSCLC. The overall HRQL results from the Crino et al. study did favor the gefitinib arm, with greater percentage of patients improved on the TOI-L and FACT-L, and the overall Lung Cancer Symptom (LCS) improvement rates were similar with gefitinib and vinorelbine. Single-agent erlotinib did not result in better HRQL or symptom control than the other treatment arms in our study. However, the HRQL and symptom improvement rates in our trial seemed to be much lower than those observed in previous trials of single-agent EGFR TKI therapy.[21,27]

The combination of gemcitabine and erlotinib did not reach the predefined threshold for further study either, based on 6-month PFS rate. The combined treatment arm seems to have resulted in a better lung cancer symptom profile by cycle 3, but it was also associated with a numerically higher rate of grade ≥3 toxicity. Four other age-unspecified phase III trials of platinum-based chemotherapy with and without EGFR TKI therapy did not reveal an improvement in PFS or OS with the addition of an EGFR TKI in the intent-to-treat patient population.[28–31] The data from these trials and our trial indicate that it is unlikely that the combination of chemotherapy and EGFR TKI therapy will result in an improvement in treatment efficacy in an unselected patient population.

It is possible that a more morbid patient population was enrolled in our trial; if so, it may also help to explain the lower HRQL and symptom response rates in all arms of this trial, compared with others that have used the same response criteria.[18,22] Stable comorbidities that are common in the elderly, such as congestive heart failure and chronic obstructive pulmonary disease, could make it unlikely that physical and FWB and pulmonary symptoms would improve to a great extent.

The 6-month PFS and median OS observed in our trial with single-agent gemcitabine are similar to the 6-month PFS and OS observed in the trial by Gridelli et al.[11] More recently, a phase III trial by Quoix et al.[32] compared single therapy (gemcitabine or vinorelbine) with carboplatin and weekly paclitaxel in patients with advanced NSCLC age 70 to 89 years. A statistically significant superior PFS and OS were observed among patients in the double agent arm compared with the single-agent arm. The PFS and OS observed in the single-agent arm are similar to the PFS and OS observed in the gemcitabine alone arm in our trial. In the trial by Quoix et al., among patients receiving single-agent gemcitabine ($n = 149$), the rate of grade 3 or 4 neutropenia (4.7%), febrile neutropenia (0%), anemia (2%), and thrombocytopenia (1.3%) was similar to the frequency of these toxicities in our trial. In our trial, the only nonhematologic toxicity observed at a rate of ≥5% among patients in the gemcitabine arm was fatigue. Thus, the efficacy and toxicity of gemcitabine are similar between the two trials, and there is no suggestion that the single-agent gemcitabine arm "underperformed" in our trial. The data from the trial by Quoix et al. suggest that for appropriate elderly patients, double-agent chemotherapy is the preferred treatment. Although there is often a concern about the use of chemotherapy doublets in older patients, we previously demonstrated in a retrospective analysis that patients older and younger than 70 years had comparable HRQL changes across 6 months when treated with a regimen of paclitaxel and carboplatin.[33]

Elderly specific trials enroll an older patient population than age unspecified trials.[9] Many "fit" elderly patients seen the participating centers may have been enrolled in trials of platinum-based therapy or treated with platinum-based therapy outside a clinical trial,[5] and the older and more morbid patients may have been enrolled in our trial. The percentage of patients receiving further therapy at the time of disease progression in arms A, B, and C was 43, 24, and 18%, respectively. It is difficult to determine the reasons for the low rate of second-line therapy in our trial. The low rate of second-line therapy may have contributed to the modest OS observed on this trial or may reflect the inherent prognosis of advanced NSCLC in this patient population. In the trial by Quoix et al., patients in both arms were offered erlotinib at the time of disease progression as a part of the trial design, and the data on the rate of second-line therapy will be of interest.

In summary, the results of our trial indicate that neither single-agent erlotinib or in combination with gemcitabine warrant further investigation in an unselected elderly patient population.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
3. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;24:4539–4544.
4. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452–462.
5. Azzoli CG, Baker S Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009;27:6251–6266.
6. Havlik RJ, Yancik R, Long S, et al. The National Institute on Aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. *Cancer* 1994;74:2101–2106.
7. Pallis AG, Gridelli C, van Meerbeeck JP, et al. EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts' opinion for the treatment of non-small-cell lung cancer in an elderly population. *Ann Oncol* 2010;21:692–706.
8. Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. *J Clin Oncol* 2007;25:5570–5577.
9. Jatoi A, Hillman S, Stella P, et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. *J Clin Oncol* 2005;23:9113–9119.
10. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. *J Natl Cancer Inst* 1999;91:66–72.
11. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003;95:362–372.
12. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small cell lung cancer. *J Clin Oncol* 2000;18:2529–2536.
13. Jackman DM, Yeap BY, Lindeman NI, et al. Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. *J Clin Oncol* 2007;25:760–766.
14. Simon GR, Extermann M, Chiappori A, et al. Phase 2 trial of docetaxel and gefitinib in the first-line treatment of patients with advanced nonsmall-cell lung cancer (NSCLC) who are 70 years of age or older. *Cancer* 2008;112:2021–2029.
15. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960–1966.
16. 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* 2000;92:205–216.
17. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 1992;41:237–248.
18. Cella D, Tulsky D, Gray G. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–579.
19. Cella D, Bonomi A, Lloyd S, et al. Reliability and validity of the of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199–200.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
21. Cella D, Herbst RS, Lynch TJ, et al. Clinically meaningful improvement in symptoms and quality of life for patients with non-small-cell lung cancer receiving gefitinib in a randomized controlled trial. *J Clin Oncol* 2005;23:2946–2954.
22. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
23. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
24. 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* 2010;11:121–128.
25. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses from a

phase III, randomized, open-label, first-line study of gefitinib (G) versus carboplatin/paclitaxel (C/P) in clinically selected patients (pts) with advanced non-small cell lung cancer (NSCLC) in Asia (IPASS). *J Clin Oncol* 2009;27(suppl):abstract 8006.
26. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
27. Crino L, Cappuzzo F, Zatloukal P, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. *J Clin Oncol* 2008;26: 4253–4260.
28. 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* 2004;22:785–794.
29. 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* 2005;23:5892–5899.
30. 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* 2007;25:1545–1552.
31. 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* 2004;22:777–784.
32. Quoix EA, Oster J, Westeel V, et al. Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2010;28:2.
33. Hensing TA, Peterman AH, Schell MJ, et al. The impact of age on toxicity, response rate, quality of life, and survival in patients with advanced, stage IIIB or IV nonsmall cell lung carcinoma treated with carboplatin and paclitaxel. *Cancer* 2003;98:779–788.

