Original Article

Gefitinib Versus Pemetrexed as Second-Line Treatment in Patients With Nonsmall Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy (KCSG-LU08-01)

An Open-Label, Phase 3 Trial

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BACKGROUND: Gefitinib was compared with pemetrexed as second-line therapy in a clinically selected population previously treated with platinum-based chemotherapy. **METHODS:** A phase 3 trial of gefitinib (250 mg/day) versus pemetrexed (500 mg/m^2 on day 1, every 3 weeks) was conducted in patients who had never smoked and who had advanced pulmonary adenocarcinoma treated with 1 previous platinum-based regimen. The primary endpoint was progression-free survival (PFS). **RESULTS:** A total of 135 patients were analyzed. The gefitinib group had significantly longer PFS compared with the pemetrexed group, with a median PFS time of 9.0 versus 3.0 months ($P = .0006$). The objective response rates were 58.8% and 22.4% for gefitinib and pemetrexed, respectively ($P < .001$). However, there was no statistically significant difference in overall survival between the 2 groups (22.2 vs 18.9 months; $P = .37$). The difference of PFS was increased in a subgroup analysis of 33 patients with activating epidermal growth factor receptor mutation (15.7 vs 2.9 months; hazard ratio, 0.3; 95% confidence interval, 0.13-0.72; $P = .005$), with numerical superiority of gefitinib in the 38 patients testing negative for epidermal growth factor receptor mutation (5.9 vs 2.7 months; $P = .099$). Both regimens were well tolerated. There were no significantly different changes in quality of life between the 2 groups, except that symptom scores for dyspnea and diarrhea favored the gefitinib and pemetrexed arms, respectively. **CONCLUSIONS:** Gefitinib showed superior efficacy to pemetrexed as second-line therapy in Korean never-smokers with pulmonary adenocarcinoma. ***Cancer*** **2012;118:6234-42.** © *2012 American Cancer Society.*

KEYWORDS: gefitinib, pemetrexed, nonsmall cell lung cancer.

Inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase, such as gefitinib or erlotinib, have been shown to prolong progression-free survival (PFS) compared with standard cytotoxic chemotherapy when given as first-line therapy in patients with advanced nonsmall cell lung cancer (NSCLC) who harbor activating EGFR mutation (deletion in exon 19 or Leu858Arg [L858R] mutation in exon 21).[1-5] Based on these data, first-line gefitinib was approved in March 2010 in Korea for the treatment of patients with NSCLC who harbor the EGFR mutation, because the therapeutic was initially approved in 2003 for the treatment of advanced NSCLC after failure of previous chemotherapy.

In routine clinical practice, however, obtaining information on EGFR mutational status is not always feasible and can be time-consuming for first-line gefitinib therapy. Therefore, many patients still receive first-line platinum-based chemotherapy, with gefitinib sometimes reserved as second-line therapy, based on the previously demonstrated efficacy of gefitinib as second-line therapy in unselected patients with NSCLC.[6-8] In addition, none of the phase 3 studies have demonstrated an overall survival benefit of EGFR tyrosine kinase inhibitors (TKIs) compared with cytotoxic chemotherapy as

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first-line therapy, which may possibly be attributed to the cross-over in poststudy treatment in these studies, with many patients initially randomized to chemotherapy receiving EGFR TKIs as second-line therapy after disease progression.

Gefitinib has been shown to be more effective in certain clinically selected populations, including patients with pulmonary adenocarcinoma, never-smokers, or patients of Asian origin. This phenomenon may be because these populations are more likely to have tumors harboring EGFR mutations.[1,9-11] According to a recently published study, positive rates for activating EGFR mutation was 75.0% in resected pulmonary adenocarcinoma from East Asian never-smokers.[11]

Pemetrexed was also approved for the treatment of advanced NSCLC after failure of prior platinum-based chemotherapy, on the basis of results of a phase 3 trial that showed this agent had a more tolerable toxicity profile with noninferior efficacy compared with docetaxel.[12] Interestingly, pemetrexed was more effective in patients with pulmonary adenocarcinoma compared with those with squamous cell carcinoma.[12,13] The histotype-dependent activity of pemetrexed, combined with the fact that adenocarcinoma itself is strongly associated with EGFR mutation,[9,10] suggests that patients with pulmonary adenocarcinoma who failed to improve with platinum-based chemotherapy are more likely to benefit from gefitinib or pemetrexed.

On the basis of these observations, we conducted a phase 3 trial to compare gefitinib with pemetrexed as second-line therapy in a clinically selected population (never-smoker Korean patients with pulmonary adenocarcinoma) who had previously received platinum-based chemotherapy for advanced NSCLC.

MATERIALS AND METHODS

Patients

This was a prospective, randomized, open-label, multicenter, phase 3 trial using the following eligibility criteria: histologically or cytologically confirmed pulmonary adenocarcinoma that progressed after just 1 previous platinum-based chemotherapy regimen for advanced disease; never-smoker (a total of $\leq$100 cigarettes in their lifetime); 18 years or older; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; measurable or evaluable disease; and adequate bone marrow, renal, and hepatic function. Patients with prior EGFR TKI or pemetrexed treatment, and symptomatic or uncontrolled brain metastases were ineligible. The protocol was approved by the institutional review boards of each institution, and all patients provided written informed consent before treatment; separate consent for assessment of EGFR gene mutation was obtained.

Study Design and Treatment Plan

Eligible patients were randomly assigned (1:1) to receive either gefitinib or pemetrexed. Patients were consecutively assigned to either the gefitinib arm or the pemetrexed arm according to a predefined computer-generated randomization scheme developed by statisticians (S.J.J., J.W.L.). Patient randomization was stratified by ECOG PS (0 or 1 vs 2) and sex (female vs male). Patients received either 250 mg/day of gefitinib orally (1 cycle for 21 days) or 500 mg/m^2 of pemetrexed as a 10-minute intravenous infusion on day 1 of a 21-day cycle. Cycles were repeated until disease progression, unacceptable toxicity, or until the patient or the investigator requested therapy discontinuation. After progression, cross-over to the alternative treatment regimen was recommended. Patients on the pemetrexed arm received oral folic acid (1 mg) daily and a vitamin B12 injection (1000 μg) every 9 weeks, beginning 1 week before the first dose and continuing until 3 weeks after the last dose of study treatment. Patients on the pemetrexed arm were prescribed to take dexamethasone (4 mg orally twice daily the day before, the day of, and the day after pemetrexed) as a prophylactic measure against skin rash.

The objective tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) every 2 cycles of therapy. The archived image scans were also reviewed by the central review team to independently assess the objective response rate. PFS was defined as the time from randomization until documented progression or death from any cause and was censored at the date of the last follow-up visit for patients who were still alive and who had not progressed. Overall survival was defined as the time from the date of randomization to date of death due to any cause. Patients who were alive on the date of last follow-up were censored on that date. Toxicity evaluations were based on Common Terminology Criteria for Adverse Events, version 3. Quality of life was assessed at baseline and then every 6 weeks with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (EORTC QLQ-C30).[14]

EGFR gene mutations were analyzed by direct gene sequencing of exons 18 through 21 of chromosome 7, if paraffin-embedded archival tumor tissue was available. Tumors harboring in-frame deletion in exon 19 or the exon 21 mutation L858R were regarded as positive for

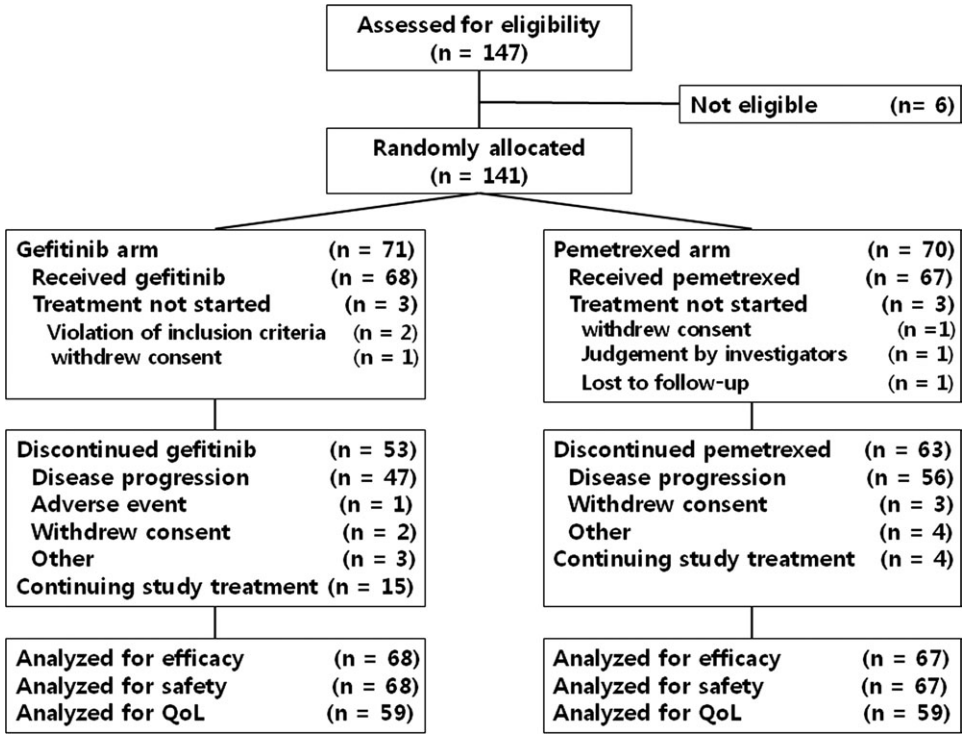

Figure 1. Algorithm is shown for patient disposition during this study. QoL indicates quality of life.

EGFR mutation, because these mutations are most clearly associated with TKI response.[9,15]

Statistical Analysis

The primary objective of the study was to compare PFS between patients who received at least 1 dose of study medication in the 2 treatment arms. Assuming that median PFS of the pemetrexed and gefitinib arms are 4 months and 6 months, respectively, PFS hazard ratio would be 0.67. A total of 152 patients with PFS events would provide 80% power to detect superiority of median PFS of the gefitinib arm with a 0.05 one-sided significance by using a log-rank test. If an enrollment period is set for 24 months and the last patient is followed for 6 months with a 10% patient drop-out rate, then 110 patients per arm are required. The log-rank test was used to compare PFS and overall survival between the treatment arms. Kaplan-Meier estimates were used to assess the median time-to-event parameters. Planned subgroup analyses were also performed to compare PFS between 2 treatment groups according to sex, age at randomization ($<$65 years or $\geq$65 years), ECOG PS (0, 1, or 2), disease stage at screening (stage IIIB or IV), and EGFR mutation status (positive, negative, or unknown).

Secondary objectives were to compare overall survival, objective response rates, safety, and quality of life. The objective response rates were compared by using the chi-square test. Regarding the analysis of quality of life, we compared the changes in quality-of-life score from baseline to the 6-week follow-up for each category between the gefitinib and pemetrexed groups. Quality-of-life scores were also assessed for statistical significance by analysis of covariance with baseline score as a covariate. We also compared PFS for cross-over therapy, in which PFS was defined as the time from the date of starting the alternative treatment to the date of documented progression or death due to any cause. The cross-over analysis was no longer a randomized comparison, but only the exploratory comparison. All reported *P* values are 2-sided except for primary endpoint analysis.

This study is registered at ClinicalTrials.gov, identifier NCT01066195.

RESULTS

Patient Characteristics

From July 2008 to June 2010, a total of 141 patients were recruited and randomized from 18 centers in Korea. The enrollment of patients was stopped early because of slow enrollment rates after pemetrexed-cisplatin and gefitinib were approved in Korea as first-line therapy in March 2010. Among 141 randomized patients, 135 patients

Table 1. Patient demographics and disease characteristics

Characteristic	Gefitinib (n = 68)	Pemetrexed (n = 67)
Median age, y (range)	58 (40-77)	64 (30-78)
Sex		
Male	10 (14.7%)	10 (14.9%)
Female	58 (85.3%)	57 (85.1%)
ECOG performance status		
0, 1	62 (91.2%)	61 (91.0%)
2	6 (8.8%)	6 (9.0%)
Stage		
IIIB	6 (8.8%)	6 (9.0%)
IV	62 (91.2%)	61 (91.0%)
Best response to first-line chemotherapy		
Complete response	0	1 (1.5%)
Partial response	28 (41.2%)	25 (37.3%)
Stable disease	26 (41.8%)	28 (41.8%)
Progressive disease	11 (16.2)	9 (13.4%)
No data	0	1 (1.5%)
Adjuvant chemotherapy within 6 months	3 (4.4%)	3 (4.5%)
EGFR mutation		
Activating mutation[a]	16 (23.5%)	17 (25.4%)
Other mutation[b]	3 (4.4%)	4 (6.0%)
Wild-type	15 (22.1%)	16 (23.9%)
Unknown mutation status	34 (50.0%)	30 (44.8%)

ECOG indicates Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

[a] Deletion in exon 19 or L858R in exon 21.

[b] S720F in exon 18, L861Q in exon 21, and duplication c.2300-2308 CCAGCGTG in exon 20 in the gefitinib arm; 2 cases of G719A in exon 18, duplication c.2323-2329 TGCCGCCTG in exon 20, and complex mutation with insertion GTT to c.2309-2311 and P772H in exon 20 in the pemetrexed arm.

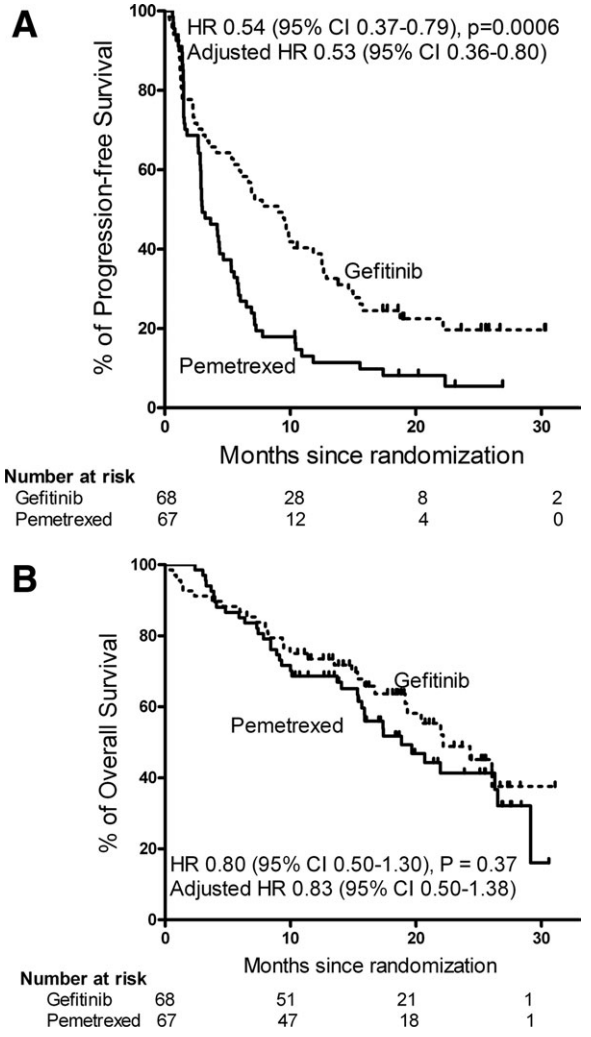

Figure 2. Kaplan-Meier curves are shown for (A) progression-free survival and (B) overall survival in the overall population. CI indicates confidence interval; HR, hazard ratio.

were actually treated with gefitinib (n = 68) or pemetrexed (n = 67), and it was a target population of analyses for efficacy and safety (Fig. 1). Clinical data cutoff was May 9, 2011. The treatment groups were well balanced for baseline characteristics including sex, ECOG PS, stage, and positive rates of EGFR mutation, with the exception of age, which tended to be lower in the gefitinib arm compared with the pemetrexed arm (Table 1). Most patients were female (85%) and had an ECOG PS of 0 or 1 (91%).

Efficacy

The median follow-up was 15.9 months and a total of 114 disease progressions or deaths had occurred (52 and 62 in gefitinib and pemetrexed arms, respectively). The median PFS for gefitinib was 9.0 versus 3.0 months for pemetrexed (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.37-0.79; $P = .0006$; 2-sided $P = .0013$; Fig. 2A). After adjusting for other clinical factors such as age, sex, and ECOG PS, gefitinib was also superior to pemetrexed for PFS with a HR of 0.53 (95% CI, 0.36-0.80). In subgroup analysis, the HR for PFS numerically favored gefitinib therapy for most subgroups except for males (Fig. 3).

The objective response rate of gefitinib therapy was significantly higher than that of pemetrexed therapy (58.8% vs 22.4%, $P < .001$). By the independent review, the response rates of each arm were 45.6% and 28.4%, respectively ($P = .038$).

The median overall survival was 22.2 months and 18.9 in the gefitinib and pemetrexed arm, respectively, and it was not significantly different (HR, 0.80; 95% CI, 0.50-1.30; $P = .37$; Fig. 2B).

At the time of analysis, 116 patients (53 and 63 in the gefitinib and pemetrexed arms, respectively) were off-

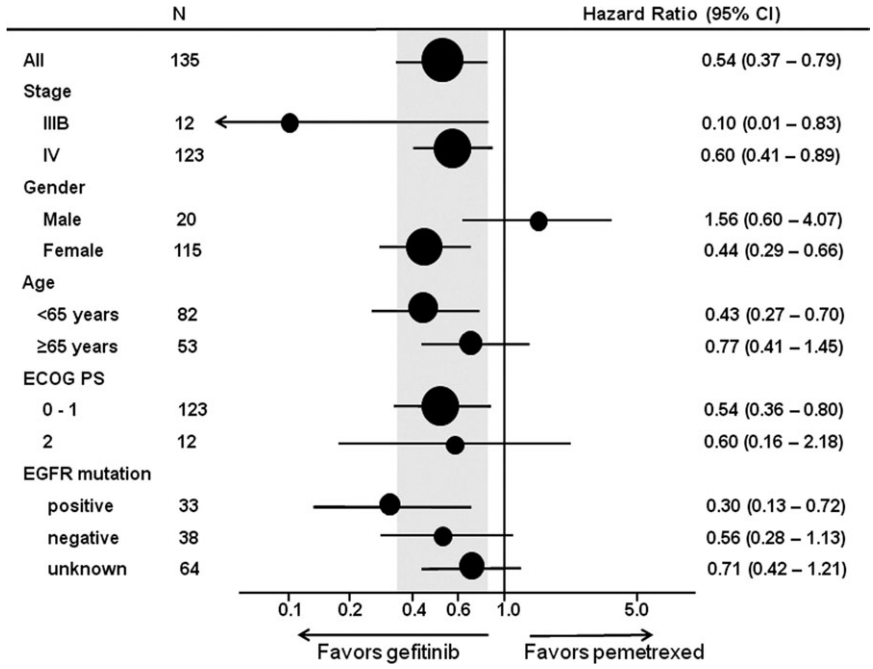

Figure 3. Subgroup analysis is shown for progression-free survival. The shaped band represents the 95% confidence interval (CI) of the hazard ratio for the overall population of patients. ECOG PS indicates Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio.

study due to disease progression, adverse event, consent withdrawal, or other causes (Fig. 1). Among these, 41 (77.4%) and 57 patients (90.5%) received salvage systemic chemotherapy in the gefitinib and pemetrexed arms, respectively. In addition, 37 of 53 patients (69.8%) in the gefitinib arm and 41 of 63 patients (65.1%) in the pemetrexed arm were crossed-over to either pemetrexed or gefitinib, respectively, as third-line therapy. Although we cannot determine which was better because of its nonrandomized nature, it showed that third-line gefitinib therapy had longer PFS than third-line pemetrexed therapy (4.5 vs 2.7 months, respectively).

Safety

Table 2 lists the most common adverse events. Hematologic adverse events were rare in both the gefitinib and pemetrexed arms, consistent with previous studies.[6,12] According to our expectations, acneiform rash (45.6%), pruritus (30.9%), and diarrhea (26.5%) were more frequently seen in the gefitinib arm compared with the pemetrexed arm. However, grade 3/4 toxicities were noted in less than 3% of patients in both arms. Serious adverse events occurred in 19.1% of the patients treated with gefitinib and 14.9% of the patients treated with pemetrexed. There was 1 adverse event (interstitial pneumonitis) leading to study withdrawal in the gefitinib arm, but none in the pemetrexed arm. However, there was no treatment-related death in either arm.

Quality of Life

A total of 132 patients (97.8%) answered the quality-of-life questionnaire at baseline, with paired data (both at baseline and a 6-week follow-up) available for 118 patients (87.4%): 59 in the gefitinib and 59 in the pemetrexed arm, respectively. The comparison of quality-of-life was performed in these patients (Table 3).

Among the parameters of global health status and functional scales, there was no significant difference between the 2 arms. Among the parameters of symptom scales, there were significant improvements in dyspnea ($P = .004$) and worsening of diarrhea scores ($P = .008$) observed in the gefitinib arm compared with the pemetrexed arm. No other significant differences in symptom scales were observed between the 2 arms.

Exploratory Analysis According to EGFR Mutation Status

Seventy-one of 135 patients (52.6%) were assessable for EGFR gene mutation. Among these patients, 33 (46.5%) were positive for EGFR gene mutation (n = 19: deletion in exon 19, n = 14: L858R mutation). Seven patients had rare types of EGFR mutation (S720F in exon 18, L861Q in exon 21, and duplication c.2300-2308 CCAGCGTG

Table 2. Hematologic and Nonhematologic Adverse Events, Those Occurring in at Least 10% of Patients in Either Treatment Group

Adverse Event	% of Gefitinib Patients (n = 68)		% of Pemetrexed Patients (n = 67)	
	Any Grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	0	0	1 (1.5%)	1 (1.5%)
Thrombocytopenia	0	0	1 (1.5%)	0
Acneiform rash	31 (45.6%)	1 (1.5%)	3 (4.5%)	0
Pruritus	21 (30.9%)	0	6 (9.0%)	0
Cough	25 (36.8%)	0	24 (35.8%)	0
Dyspnea	13 (19.1%)	0	18 (26.9%)	0
Chest pain	12 (17.6%)	0	20 (29.9%)	1 (1.5%)
Interstitial pneumonitis	1 (1.5%)	1 (1.5%)	0	0
Sensory neuropathy	11 (16.2%)	0	7 (10.4%)	0
Infection	11 (16.2%)	1 (1.5%)	4 (6.0%)	2 (3.0%)
Fatigue	15 (22.1%)	0	14 (20.9%)	0
Anorexia	22 (32.4%)	1 (1.5%)	20 (29.9%)	0
Nausea	11 (16.2%)	0	11 (16.4%)	0
Diarrhea	18 (26.5%)	0	3 (4.5%)	0
Constipation	5 (7.4%)	0	10 (14.9%)	0
Dizziness	5 (7.4%)	0	8 (11.9%)	0

The grades were defined according to the Common Terminology Criteria for Adverse Events.

Table 3. Differences in Quality of Life During 6 Weeks Follow-Up Between Patients Receiving Gefitinib and Pemetrexed

Parameter	Gefitinib[a]		Pemetrexed[b]		Between-Arm Difference[c] (n_{max} = 59)	*P*
	Baseline (n_{max} = 66)	Follow-Up (n_{max} = 60)	Baseline (n_{max} = 66)	Follow-Up (n_{max} = 60)		
Global health status	56.2 (20.1)	57.9 (23.2)	53.0 (21.7)	55.0 (24.5)	1.1 (–6.7 to 8.9)	0.78
Function scales						
Physical	71.4 (18.5)	72.7 (21.5)	68.5 (20.9)	71.7 (21.5)	–0.5 (–7.1 to 6.2)	0.89
Role	66.9 (27.8)	68.3 (29.2)	66.9 (22.9)	63.9 (26.4)	5.0 (–3.6 to 13.5)	0.25
Emotional	74.0 (20.9)	79.3 (21.6)	70.3 (19.9)	75.8 (24.0)	1.4 (–6.2 to 8.9)	0.72
Cognitive	81.6 (17.6)	81.9 (18.2)	75.8 (20.7)	76.7 (19.2)	3.4 (–2.7 to 9.5)	0.27
Social	69.7 (26.8)	74.2 (29.8)	69.7 (26.6)	72.9 (28.2)	2.0 (–7.7 to 11.8)	0.68
Symptom scales						
Fatigue	34.0 (19.9)	36.9 (24.1)	38.2 (22.1)	36.5 (24.0)	2.1 (–6.0 to 10.2)	0.60
Nausea/vomiting	13.4 (21.5)	13.9 (21.5)	14.1 (21.1)	10.0 (16.3)	4.8 (–4.0 to 13.7)[d]	0.28
Pain	27.5 (24.7)	23.3 (28.5)	28.8 (26.1)	28.3 (29.6)	–5.8 (–15.0 to 3.4)	0.22
Dyspnea	25.3 (24.8)	18.9 (24.8)	34.3 (29.2)	35.6 (31.2)	–12.8 (–21.4 to 4.1)	0.004
Insomnia	21.7 (26.5)	21.1 (28.1)	29.8 (31.6)	32.8 (30.4)	–9.3 (–19.1 to 0.5)	0.06
Appetite loss	28.8 (30.9)	24.4 (32.4)	38.4 (31.1)	22.8 (28.5)	12.4 (–1.2 to 26.0)[d]	0.07
Constipation	20.7 (26.0)	10.0 (18.7)	15.2 (22.8)	10.6 (18.9)	–1.7 (–8.2 to 4.8)	0.60
Diarrhea	5.6 (13.8)	14.4 (19.8)	7.6 (19.2)	6.1 (14.4)	8.5 (2.2 to 14.9)	0.008
Financial problems	29.8 (26.9)	24.4 (28.0)	27.8 (29.6)	31.1 (29.6)	–8.3 (–16.9 to 0.4)	0.06

Data are mean (standard deviation) or mean difference (95% confidence interval). n_{max} = maximum number of patients with available data.
[a] A total of 63 to 66 patients had data at baseline, 60 patients had data at follow-up, and 56 to 59 patients had data at baseline and follow-up.
[b] A total of 64 to 66 patients had data at baseline, 58 to 60 patients had data at follow-up, and 55 to 59 patients had data at baseline and follow-up.
[c] Value for gefitinib during follow-up minus pemetrexed during follow-up (positive values in global health status and function scales, and negative values in symptom scales favor gefitinib), based on estimated marginal means with baseline values as covariates; n_{max} = 59 for gefitinib and pemetrexed arms, respectively.
[d] Difference represents the change in scores from baseline to follow-up in the gefitinib arm minus the pemetrexed arm because of violation of the assumption of equality of error variances in the covariance analysis.

in exon 20 in the gefitinib arm; 2 cases of G719A in exon 18, duplication c.2323-2329 TGCCGCCTG in exon 20, complex mutation with insertion GTT to c.2309-2311 and P772H in exon 20 in the pemetrexed arm). Both the rare types and wild-type for EGFR were regarded as negative for EGFR mutation. Mutation status was well-balanced between the treatment arms; 47.1% (16 of 34 patients) in the gefitinib arm and 45.9% (17 of 37

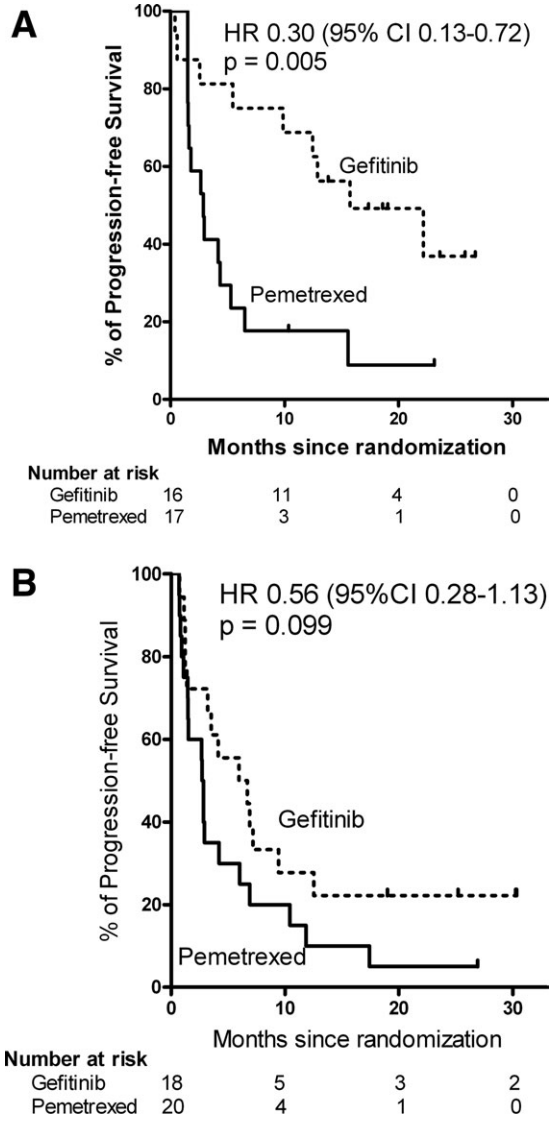

Figure 4. Progression-free survival in (A) the positive group for epidermal growth factor receptor (EGFR) mutation and in (B) the negative group for EGFR mutation. CI indicates confidence interval; HR, hazard ratio.

patients) in the pemetrexed arm had tumors harboring EGFR mutations ($P = .93$).

The median PFS for gefitinib and pemetrexed therapy in a subgroup with positive EGFR mutation status were 15.7 and 2.9 months, respectively (HR, 0.30; 95% CI, 0.13-0.72; $P = .005$; Fig. 4A). Among patients who were negative for EGFR mutation, the median PFS for gefitinib and pemetrexed therapy were 5.9 and 2.7 months, respectively (HR, 0.56; 95% CI, 0.28-1.13; $P = .099$; Fig. 4B). Among patients with unknown EGFR mutation status, the median PFS for the gefitinib and pemetrexed arms were 7.8 and 4.4 months, respectively (HR, 0.71; 95% CI, 0.42-1.21; $P = .21$).

The objective response rates of gefitinib in subgroups with EGFR mutationpositive and EGFR-negative tumors were 87.5% and 38.9%, respectively ($P = .004$). By the independent review, the response rates of each subgroup were 68.8% and 27.8%, respectively ($P = .017$).

DISCUSSION

Both gefitinib and pemetrexed are known to be effective as second-line therapy for NSCLC. This study shows that gefitinib is superior to pemetrexed as second-line therapy for NSCLC in a clinically selected population of Korean patients.

In this study, after failure of platinum-based first-line chemotherapy, gefitinib significantly prolonged PFS and increased objective response rates compared with pemetrexed therapy in Korean never-smokers with pulmonary adenocarcinoma. However, the prolongation of PFS in the gefitinib arm compared to the pemetrexed arm did not translate into a survival difference. This may be attributed to the fact that most patients (83.8%) received additional treatment after protocol discontinuation, which could offset the difference of PFS between 2 groups. Furthermore, 61.2% (41 of 67 patients) of the pemetrexed arm received third-line therapy with gefitinib. Given the high rates of poststudy treatment, the difference of 3.3 months (22.2 vs 18.9 months) in overall survival cannot be negligible in second-line therapy, even though it was not statistically significant. There were no significant differences in toxicity profiles between the 2 arms: both gefitinib and pemetrexed were well tolerable as shown previously in other studies.[1-3,12] Although there were no significantly different changes in most quality-of-life categories from baseline to 6 weeks after starting treatment in both arms, dyspnea improved and diarrhea worsened more in the gefitinib arm compared with the pemetrexed arm. Given the prolonged PFS, tolerable toxicity, and no deterioration of quality of life in gefitinib arm, it suggests that gefitinib can be considered prior to pemetrexed in a clinically selected population after failure of first-line platinum-based chemotherapy.

The distribution of EGFR mutation status was well balanced between the 2 groups in our study, even though patients were not randomized according to EGFR mutation status. It implies that the superior efficacy of gefitinib was less likely caused by the skewed distribution of genetic characteristics between arms. In addition, the superiority of gefitinib was verified again by the cross-over analysis, where third-line gefitinib therapy also showed superior efficacy to third-line pemetrexed when 2 drugs were administered to patients in the opposite arms. However, we

should be cautious in the interpretation of the cross-over analysis, because it was not a randomized comparison.

It is notable that the efficacy of gefitinib therapy in a subgroup of individuals who were negative for EGFR mutation was better than expected, given the results of the IPASS (Iressa Pan-Asia Study) trial (response rates of 1.1%). A possible explanation is the difference of method for detecting EGFR mutations between 2 studies. We used direct sequencing, which is regarded as less sensitive than the ARMS (amplification-refractory mutation system) method, which was used in the IPASS trial.[1,16] Even though clinical characteristics of the population between 2 studies were very similar, except that IPASS also included approximately 6% of former light smokers, the proportion of patients with deletion in exon 19 or L858R mutation was 46.5% in our study, which was lower than the positive rate (57.4%) in the IPASS study. In addition, according to another study performed with surgical specimens, activating the EGFR mutation was observed in 75.0% of resected pulmonary adenocarcinoma from Asian patients who have never smoked.[11] Therefore, many tumors regarded as negative for EGFR mutation in our study could turn out to be positive with the more sensitive technique. This explanation is supported by similar results of a molecular study from another Korean clinical trial (First-SIGNAL), which enrolled never-smokers with pulmonary adenocarcinoma and evaluated EGFR mutation with direct sequencing: among 96 evaluable cases for EGFR mutation analysis, 54 (56.2%) were negative for EGFR mutation, and the response rates of this group was 25.6%, which was consistent with our results.[17] Therefore, these 2 Korean studies, as well as ours, signify the importance of considering sensitivity of EGFR mutation tests when interpreting EGFR mutation results.

During the study period, pemetrexed-cisplatin and gefitinib were approved as first-line therapy for a selective NSCLC population in Korea, and it lead to early closure of this study. Nevertheless, this study is notable because it is a well-designed phase 3 trial and met the primary endpoint. Although both pemetrexed and gefitinib are considered good therapeutic options as first-line therapy, these 2 agents are also widely used as second-line therapy because of several practical reasons: insufficient specimens for performing EGFR mutation test; no time to wait for data on EGFR mutation or waiting for 1 to 2 weeks of vitamin premedication before pemetrexed therapy, especially in symptomatic or rapidly progressing patients; and finally, the belief of the clinical relevance of pemetrexed and gefitinib as second-line therapy by treating physician in terms of patient survival.

In the subgroup analysis, males were less likely to benefit from gefitinib than pemetrexed. Although definitive conclusions cannot be made due to the small number ($n = 20$) of male patients in our study, some plausible explanations can be suggested. There is a study supporting the reverse relationship between rates of positive EGFR mutation and males: rates of positive EGFR mutation in men were lower than those in women (63.6% vs 82.9%), even among never-smoker Asian patients with pulmonary adenocarcinoma.[11]

Although EGFR mutation status is the strong predictive factor for therapy with EGFR TKIs, it is not so easy to obtain sufficient tumor specimen for EGFR mutation analysis. Only approximately half of our patients were successfully analyzed for EGFR mutation, even though we made much effort. The testing rates for EGFR mutation across East Asian nonsquamous patients is thought to be similar to our results,[18] which implies that the therapeutic decision should be made without genotype information in at least 50% of patients with NSCLC. In that sense, it is important that regimen be selected as second-line therapy without knowing EGFR mutation status, especially in a clinically enriched population. The present data might influence this decision. However, caution should be exercised in interpreting our results, because the study population was confined to patients whose tumoral EGFR mutation statuses have not been tested by more sensitive EGFR mutation testing such as the amplification-refractory mutation system or the peptide nucleic acid–locked nucleic acid PCR clamp method.

In summary, this study shows that second-line therapy with gefitinib compared with pemetrexed prolonged PFS and increased objective response rates without deterioration of quality of life in clinically selected patients with NSCLC.

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