Clinical Outcomes After First-line EGFR Inhibitor Treatment for Patients with NSCLC, *EGFR* Mutation, and Poor Performance Status

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Abstract. *Background: The phase II NEJ001 trial suggested that gefitinib was active against advanced non-small cell lung cancer (NSCLC) even in patients with poor performance status (PS). Clinical response among the patients harboring epidermal growth factor receptor (EGFR) mutation with poor PS is fair; however, gefitinib does not have as much continued efficacy as in patients with good PS. This study has retrospectively investigated the clinical outcomes of gefitinib treated patients with advanced NSCLC, EGFR mutations, and poor PS. Patients and Methods: A total of 208 patients with advanced NSCLC and poor PS treated with gefitinib from 2004 to 2013 were retrospectively evaluated. Outcomes were studied after stratification for gender, smoking status, histological subtype, and EGFR mutation status. Results: Fifty-two patients (25.0%) with advanced NSCLC, EGFR mutation, and poor PS were treated with gefitinib. The overall response rate was 65.4%. The median progression-free survival, median survival time, and one-year survival rate was 6.6 months, 19.6 months, and 62.9%, respectively. Death due to interstitial lung disease occurred in 11.5% of the patient population. In multivariate analysis, a PS of 4 was independently associated with poor outcomes (hazard ratio=10.5; 95% Confidence interval=1.92-50.19; p=0.0091). Conclusion: Patients with advanced NSCLC, EGFR mutation, and poor PS have poor outcomes in response to gefitinib. However, the indication of gefitinib for such patients will not be changed in clinical practice and oncologists should treat these patients with more careful follow-up since for those with poor PS, therapy may be more toxic than for patients with good PS.*

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Lung cancer is the leading cause of cancer death worldwide (1), mainly because most patients are diagnosed at a late stage in the disease. Chemotherapy is indicated for patients with advanced non-small cell lung cancer (NSCLC) with good Eastern Cooperative Oncology Group (ECOG) performance status (PS) and moderate reserve in organ function. By contrast, the American Society of Clinical Oncology (ASCO) recommends only the best supportive care for patients with advanced NSCLC and poor PS (2).

PS is the strongest predictor of outcome in patients with advanced NSCLC (3), and approximately 12% of all patients with lung cancer have a poor PS score of 3 or 4 (4). However, continued advancements in the field of molecularly-targeted agents has changed the PS-based indications for cytotoxic chemotherapy.

Gefitinib (Iressa; AstraZeneca, London, UK) is an orally-targeted therapy that reversibly inhibits the small molecular tyrosine kinase domain of the epidermal growth factor receptor (EGFR). Predictors of favorable response to gefitinib include East Asian ethnicity, adenocarcinoma, non-smoking or light smoking status, female sex, and somatic mutations of *EGFR* in exon 19 or 21 (5-8). However, these predictors also represent confounding factors, as they might reflect a population with a high prevalence of *EGFR* mutations. At present, the use of gefitinib for patients with advanced NSCLC, *EGFR* mutation, and good PS with adequate organ functions is associated with a response rate of 60-70%, progression-free survival (PFS) of 9-12 months, and overall survival (OS) of 25-35 months (9, 10).

Table I. *Landmark clinical trials of molecular-targeted therapy for non-small cell lung cancer harboring oncogenic driver mutation.*

Clinical trials	Eligibility	ORR (%)	mPFS (months)	mOS (months)
Gefitinib for *EGFR* mutation				
NEJ001 (n=31) (11)	PS 3,4, ≤74 years; PS 2-4, 75-79 years; PS 1-4 ≥ 80 years	66	6.5	17.8
NEJ003 (n=30) (12)	PS 0, 1, ≥80 years	74	12.3	26.9
NEJ002 (n=114) (9)	PS 0-2, ≤75 years	73.7	10.8	30.5
WJTOG3405 (n=86) (10)	PS 0-1, ≤75 years	62.1	9.2	35.5
Crizotinib for *ALK* fusion oncogene				
PROFILE1001 (n=82) (28)	PS 0-2, ≥18years	57	6.4†	Not reached
PROFILE1005 (n=261) (29)	PS 0-2, ≥18 years	59.8	8.1	Not reached
PROFILE1007 (n=173) (30)	PS 0-2, ≥18 years	65	7.7	Not reached

PS, Performance status; EGFR, epidermal growth factor receptor; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; ALK, anaplastic lymphoma kinase. †a mean treatment duration.

Furthermore, the phase II NEJ001 trial suggested that gefitinib was also active against advanced NSCLC in patients with *EGFR* mutations and poor PS (11). The advent of first-line gefitinib revived these patients with poor PS, which was called a 'Lazarus Response'. In these patients the median PFS was slightly shorter and the median survival time was much shorter compared to those with good PS (Table I). However, in the clinical setting, the response to gefitinib among patients with advanced NSCLC, *EGFR* mutations, and poor PS seems to be less favorable than what was seen in the NEJ001 trial or in phase III studies of patients with better PS. While the NEJ001 trial included elderly patients with PS 1, the NEJ003 trial showed that the efficacy of first-line gefitinib for patients with NSCLC and *EGFR* mutation was similar regardless of PS or age (12). Furthermore, the IFCT-0501 (13) and WJTOG9904 (14) trials demonstrated that cytotoxic chemotherapy has similar efficacy for advanced NSCLC when comparing elderly patients with good PS and younger patients. These data suggest that elderly patients with advanced NSCLC, *EGFR* mutation, and good PS (25%) in the NEJ001 trial had better than average therapeutic responses to gefitinib and this did not accurately reflect the outcomes that occur in patients with advanced NSCLC, *EGFR* mutations, and poor PS.

Therefore, the goal of this retrospective study was to investigate the response to gefitinib in patients with advanced NSCLC, *EGFR* mutation, and poor PS.

Patients and Methods

Patients and data acquisition. A retrospective review was performed of the databases at Tokyo Metropolitan Cancer and Infectious diseases Center at Komagome Hospital (Tokyo, Japan) to identify patients with NSCLC who were treated with gefitinib (n=208) between January 1, 2004 and July 31, 2013. Patients were included if they met the following criteria: (i) histologically or cytologically confirmed advanced (stage IIIB/IV) or recurrent NSCLC; (ii) previously untreated; (iii) ECOG PS of 2 for patients older than 75 years of age, or of 3 or 4 for patients of any age at the time of initiation of gefitinib therapy. Elderly patients (age ≥75) with good PS (0,1) who were candidates for first-line cytotoxic chemotherapy were excluded.

EGFR mutation was detected using the peptide nucleic acid (PNA)-locked nucleic acid (LNA) polymerase chain reaction (PCR) clamp method, or the Cycleave PCR method since 2008. However, some patients with poor PS were treated with first-line gefitinib as salvage therapy before 2008; thus, we retrospectively assessed *EGFR* mutation using paraffin-embedded tissues *via* the Cycleave PCR method (Figure 1). Medical records and radiographic images were also reviewed to assess the patient characteristics, response to gefitinib, and clinical outcomes. This study was approved by an Institutional Review Board (1258).

Treatment and evaluation. Patients with poor PS were treated with oral gefitinib (250 mg once daily) as first-line treatment until the onset of unacceptable toxicities or disease progression, or until patients' refusal to continue with therapy. Tumor response was usually assessed weekly for the first month and then monthly thereafter using chest radiography. Computed tomography imaging was performed at least once every two months. Clinical response was assessed *via* the Response Evaluation Criteria in Solid Tumors criteria version 1.1 (RECIST 1.1) (15). Hematological and non-hematological toxicities related to chemotherapy were described with the common toxicity criteria according to the Common Terminology Criteria for Adverse Events, version 4 (16).

Statistical analysis. The primary endpoints were clinical outcomes in patients who received at least one dose of gefitinib as first-line therapy. PFS was defined as the time from the first cycle of chemotherapy to the first clinical evidence of progressive disease (PD), early discontinuation of treatment, or death from any cause. Patients treated with gefitinib beyond PD were included in the analysis when PD was confirmed on radiographic studies. Survival time was defined as the period from the date of initiation of first-

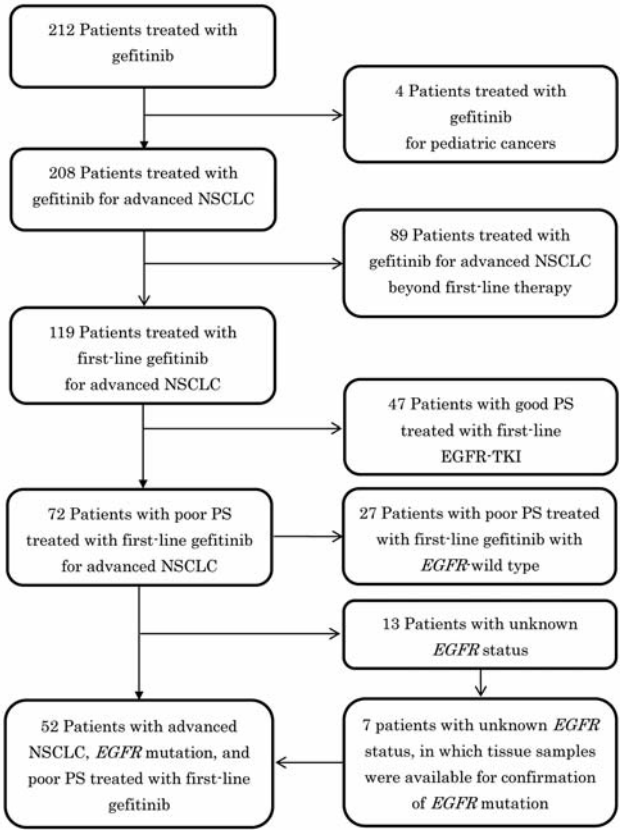

Figure 1. *Flow diagram of patient selection.*

Table II. *Patients' demographics.*

Characteristic	No. of patients (n=52)	(%)
Median age, years (range)	75 (54-87)	-
Gender		
Male	11	21.2
Female	41	78.8
ECOG-PS		
2	21	40.4
3	27	51.9
4	4	7.7
Smoking status		
Non-smoker	34	65.4
Previous/Current smoker	18	34.6
Histology		
Adenocarcinoma	48	92.3
Squamous cell carcinoma	2	3.8
Adenosquamous cell carcinoma	1	1.9
Pleomorphic carcinoma	1	1.9
Staging		
IIIB	4	7.7
IV	38	73.1
Recurrent	10	19.2
EGFR mutation		
Exon 19	23	44.3
Exon 21	29	55.7
Later lines of chemotherapy†		
Platinum-doublet	4	7.7
Single-agent	4	7.7
None	32	61.5
Under treatment	11	21.2
Erlotinib	1	1.9

No., Number; EGFR, epidermal growth factor; ECOG-PS, Eastern Cooperative Oncology Group Performance Status. †Median no. of later lines of chemotherapy was one in all patients.

line gefitinib to the date of death from any cause or last follow-up. This parameter was assessed using the Kaplan–Meier method. Patients lost to follow-up were censored at the time of last contact. The Kaplan–Meier method was used to estimate overall survival and the one-year survival rate. The log-rank test was used to identify factors that predicted survival in the univariate analysis. Analyzed variables included smoking status (non-smoker *vs.* current or previous smoker), histology (adenocarcinoma *vs.* others), stage (IIIB *vs.* IV *vs.* recurrent), PS (2 *vs.* 3 *vs.* 4) and *EGFR* mutation (exon 19 *vs.* exon 21) in univariate and multivariate analyses. Significant factors ($p<0.05$) in univariate analysis were included in the multivariate Cox proportional hazards model. Pearson's test or Fisher's exact χ^2 test was used to determine the relationship between tumor response and variables. All statistical analyses were performed using JMP9 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients' characteristics. Among 212 patients, a total of 52 patients (11 males, 41 females) with advanced NSCLC, *EGFR* mutation, and poor PS were treated with first-line gefitinib and were included in this analysis (Figure 1). Their median age was 75 years (range=54-87 years). Four patients (7.7%) had stage IIIB disease, 38 patients (73.1%) had stage IV and 10 patients (19.2%) had recurrent disease. Histological examination revealed that 48 patients had adenocarcinoma (92.3%), while the remaining patients had adenosquamous carcinoma, pleomorphic carcinoma, or squamous cell carcinoma. Patients' characteristics are shown in Table II.

Clinical outcomes in response to first-line gefitinib, and factors affecting survival. Disease control was observed in 41 patients (78.8%), with 34 showing partial response (65.4%) and seven showing stable disease (13.5%); eight patients (14.3%) had PD. There were no complete responders. The response rate was 72.3% for patients with *EGFR* mutation in exon 19 and was 58.6% for patients with EGFR mutation in exon 21. Eight patients (15.4%) were subsequently treated with cytotoxic chemotherapy (four with platinum-doublet chemotherapy) as PS improved, or were treated *via* re-administration of EGFR-TKI. The PFS for patients overall was 6.6 months [95% confidential interval (CI)=3.12-11.37 months], and the median survival time was

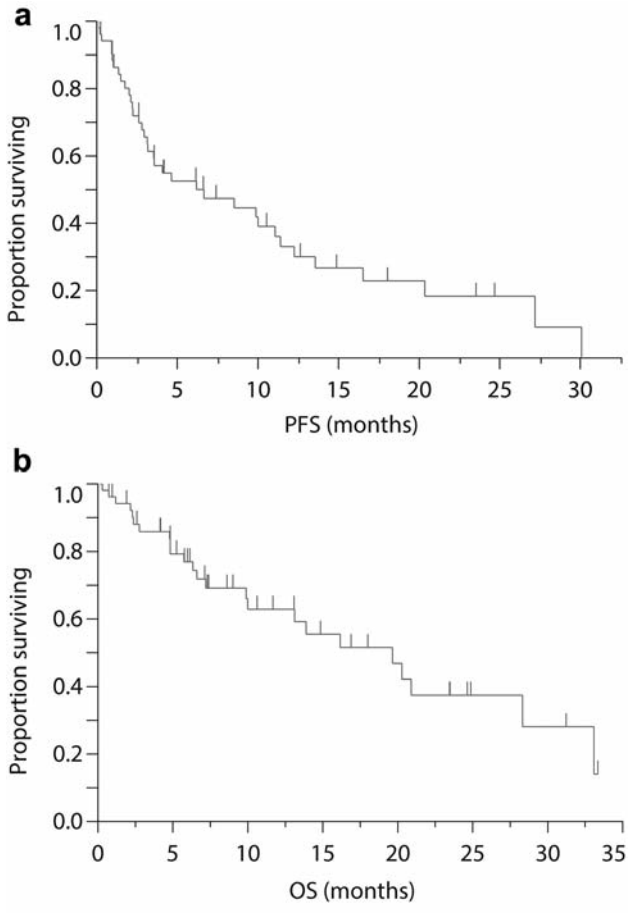

Figure 2. *Progression-free survival (a) and overall survival (b) of patients with advanced non-small cell lung cancer EGFR mutation and poor performance status treated with first-line gefitinib.*

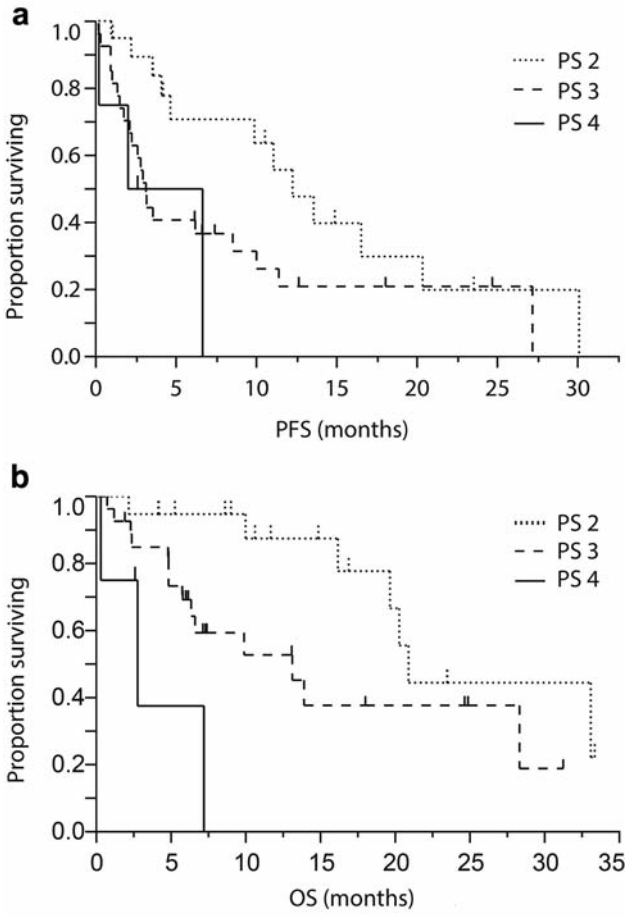

Figure 3. *Progression-free survival (a) and overall survival (b) of patients with advanced non-small cell lung cancer EGFR mutation and poor performance status treated with first-line gefitinib, as stratified by performance status.*

19.6 months (95% CI=9.8-28.3 months). The one-year survival rate was 62.9% (Figure 2). The median PFS in the subgroup analysis stratified by PS was 12.2 months (95% CI=4.63-20.30 months), 3.12 months (95% CI=1.94-8.50 months), and 4.32 months (95% CI=0.20-6.64 months) in the PS 2 group, PS 3 group and PS 4 group, respectively. Also, the median survival time was 20.9 months (95% CI=16.2-not reached), 13.1 months (95% CI=5.96-not reached) and 2.76 (95% CI=0.30-7.20 months) in PS 2 group, PS 3 group and PS 4 group, respectively. The one-year survival rate was 87.5%, in the PS 2 group, 52.8% in the PS 3 group, 0% in the PS 4 group (Figure 3).

Subgroup analysis showed superior survival in patients who had never smoked compared to smokers (p=0.02). Other factors, such as age, gender, histology, and *EGFR* mutation, did not have a significant impact on survival (Table III). In multivariate analysis, PS 4 was associated with extremely poor survival (Table IV).

Safety profile and tolerability of first-line gefitinib. Gefitinib therapy was terminated in 17 patients (32.7%) due to toxicity [six patients (11.5%) due to interstitial lung disease (ILD), three patients (5.7%) due to inability for oral intake, and three patients due to elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (5.8%)] and due to PD in 19 patients (52.8%) (Table V).

Discussion

Gefitinib was developed in the 1990s as a reversible targeted inhibitor of EGFR with the goal of specifically inhibiting cancer cell growth and preventing myelosuppression (17). Therefore, patients with advanced NSCLC and poor PS who were ineligible for cytotoxic chemotherapy were treated with gefitinib as salvage therapy. Two clinical phase II studies demonstrated that single-agent gefitinib was associated with a response rate of 9-19% and a one-year survival rate of 24-36%

Table III. *Univariate analysis of the relationship between various parameters and survival among patients with advanced non-small cell lung cancer, EGFR mutation, and poor performance status treated with first-line gefitinib.*

Variables	Cut-off	No. of patients	MST (95% CI)	*p*-Value
Smoking status	Non-smoker	34	20.3 (13.1-never smoked)	0.02*
	Current/ex-smoker	18	6.3 (2.1-28.3)	
Gender	Male	11	16.2 (2.2-28.3)	0.26
	Female	41	20.3 (9.8-not reached)	
Histology	Adenocarcinoma	48	19.6 (9.9-28.3)	0.72
	Other	4	Not reached (9.9-not reached)	
Stage	IIIB	4	Not reached (4.8-not reached)	
	IV	38	16.1 (7.2-28.3)	0.19
	Recurrent	10	Not reached (10.0-not reached)	
Performance status	2	21	20.9 (16.2-not reached)	
	3	27	13.1 (5.7-not reached)	0.002*
	4	4	2.8 (0.3-7.2)	
Performance status	Moderate (PS=2)	21	20.9 (16.2-not reached)	0.039*
	Severe (PS=3 or 4)	31	10.0 (5.7-28.3)	
EGFR mutation	Exon 19	23	20.9 (7.1-28.3)	0.25
	Exon 21	29	13.1 (9.8-28.3)	

CI, Confidence interval; MST, median survival time; No., number; EGFR, epidermal growth factor receptor. *$p<0.05$.

Table IV. *Multivariate analysis of the relationship between various parameters and survival among patients with advanced non-small cell lung cancer EGFR mutation and poor performance status treated with first-line gefitinib.*

Variables	HR	95% CI	*p*-Value
Performance status			
PS 4 *vs*. PS 3	4.15	0.86-15.55	0.072
PS 3 *vs*. PS 2	2.54	0.97-7.45	0.058
PS 4 *vs*. PS 2	10.5	1.92-50.19	0.0091*

PS, Performance status; HR, hazard ratio; CI, confidential interval. *$p<0.05$.

Table V. *Reasons for termination of first-line gefitinib.*

	Number of patients (n=36), (%)
Non-hematological	
Inability of oral intake	3 (5.7%)
Anorexia	4 (7.7%)
Elevated transaminase	3 (5.8%)
Pneumatosis coli	1 (2.9%)
ILD	6 (11.5%)
PD	19 (52.8%)

ILD, Interstitial lung disease; PD, progressive disease. No hematological toxicities were reported.

(5, 18). However, no survival benefit was demonstrated among the entire group of patients with advanced NSCLC in a clinical phase III study (19). Among patients treated with gefitinib, some were 'super-responders'. In 2004, *EGFR* mutation was discovered to be a predictor of favorable response to gefitinib (6, 20). In 2007, the IPASS study demonstrated that PFS in response to carboplatin-paclitaxel was improved among patients who never smoked or were previous light smokers, female patients, or those with adenocarcinoma in Asian countries (21). Then two landmark phase III trials, NEJ002 and WJTOG3405, also demonstrated that gefitinib was superior to platinum-doublet chemotherapy in terms of PFS. Furthermore, OS was twice as long with gefitinib when compared with previous trials of cytotoxic chemotherapy for genetically-unselected patients (22). However, among the patients who were selected and had NSCLC with poor PS and therefore were unfit for cytotoxic chemotherapy, first-line gefitinib was not effective. By contrast, first-line erlotinib (another EGFR-TKI) resulted in improved PFS but no change in OS in patients with poor PS (23). These data suggest that EGFR-TKIs should not be administered to patients who have wild-type *EGFR*.

The response rate to gefitinib for poor PS in the genetically-selected patients in this study was similar to those in the NEJ001 trial. An editorial published in the Journal of Clinical Oncology insisted that NEJ001 established definitive clinical evidence and that further phase III trials, or clinical studies that compare gefitinib and best supportive care in patients with poor PS are not required (24). Thus, additional data regarding clinical outcomes in this patient population will likely be derived only from observational studies or retrospective analyses.

Targeted inhibitors against the echinoderm microtubule-associated protein-like 4 (*EML4*) to anaplastic lymphoma kinase (*ALK*) fusion gene may also be useful in patients with *ALK*-positive NSCLC and poor PS. However, because this condition is rare (4% of all NSCLC) (25), it will take a long time to accrue patients for clinical studies to address this question. Targeted agents have been used for other types of cancer, including trastuzumab for metastatic breast cancer and advanced gastric cancer, cetuximab/panitumumab for metastatic colorectal cancer, sorafenib for hepatocellular carcinoma, or sorafenib/sunitinib/mammalian target of rapamycin inhibitors for metastatic renal cell carcinoma. Although some targeted agents have activity when given in combination with cytotoxic chemotherapy, the utility of combination therapy has not been extensively studied in patients with poor PS. In patients with metastatic renal cell carcinoma, sunitinib is less effective for patients with poor PS (response rate of 9% in the patients with more than PS 2) than in those with good PS (response rate of 17% in the group of all patients), or in patients older than 65 years of age (response rate of 17%). Moreover, in patients treated with sunitinib, PFS and OS were worse in patients with poor PS than in those with good PS (5.1 months *vs*. 10.9 months and 6.7 months *vs*. 18.4 months, respectively). Sunitinib was associated with PFS and OS of 11.3 months and 18.2 months, respectively, in elderly patients, which is comparable to outcomes seen in the general population (26). Thus, targeted agents such as EGFR-TKI for driver oncogenes may be characterized as having a similar response rate, but less PFS. The differences in the activities of targeted agents are based on carcinogenesis related to the 'addiction' of cancer cells to the driving oncogene. Therefore, OS for patients with poor PS will be short if they do not experience an improvement in PS that makes them candidates for subsequent cytotoxic chemotherapy. The shortened OS in patients with poor PS is reasonable, because there is no indication for later lines of cytotoxic chemotherapy. However, the shortened PFS in response to gefitinib in the patients with poor PS may be a finding that can be generalized to all molecularly targeted agents.

In the present study, the toxicity profile of gefitinib among patients with poor PS was more severe when compared to that experienced by patients with good PS in clinical trials, especially with regard to ILD. However, a previous study reported that ILD was 10-times more likely in patients with poor PS than in patients with good PS (27). EGFR-TKI-induced ILD occurs in 5% of Japanese patients, and 1.5% of patients with gefitinib-related ILD and good PS will die. Therefore, EGFR-TKIs should be used with caution in patients with advanced NSCLC, *EGFR* mutation, and poor PS.

This study was limited by its retrospective nature and the small sample size. The reason for which PFS in the PS 4 group was shorter than OS, may be due to the statistically too small number of cases. Additionally, there were inherent limitations in collecting toxicities, and this study did not collect data regarding quality of life (including any improvements in PS), which are some of the most important predictors of outcome in patients with poor PS. However, gefitinib still has efficacy for patients with advanced NSCLC and *EGFR* mutation regardless of PS. The present study supports the notion that *EGFR* mutation is the strongest predictor of the response to gefitinib and that PS might be a predictor of the durability of the response to gefitinib.

In conclusion, despite the reduced efficacy and increased toxicity of gefitinib in this study relative to the NEJ001 trial, we conclude that first-line gefitinib still represents a promising treatment for patients with advanced NSCLC, *EGFR* mutation, and poor PS.

Conflicts of Interests

None declared.

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