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Individual-level data on the relationships of progression-free survival, post-progression survival and tumor response with overall survival in patients with advanced non-squamous non-small cell lung cancer

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The effects of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies in patients with non-small cell lung cancer (NSCLC). We examined whether progression-free survival (PFS), post-progression survival (PPS), or tumor response could be valid surrogate endpoints for OS after first-line chemotherapies in advanced NSCLC by using individual-level data, given the lack of research in this area. Between April 2009 and June 2011, 50 patients with advanced non-squamous NSCLC treated with cisplatin and pemetrexed as first-line chemotherapy were analyzed. The relationships of PFS, PPS, and tumor response with OS were analyzed at the individual level. Spearman rank correlation analysis and linear regression analysis showed that PPS was strongly correlated with OS ($r = 0.89$, $P < 0.05$, $R^2 = 0.79$), PFS was moderately correlated with OS ($r = 0.67$, $P < 0.05$, $R^2 = 0.39$), and tumor shrinkage was weakly correlated with OS ($r = 0.36$, $P < 0.05$, $R^2 = 0.14$). Performance status at the beginning of second-line treatment, the best response to second-line treatment, and number of regimens used after progression following first-line chemotherapy were significantly associated with PPS ($P < 0.05$). Analysis of individual-level data suggested that PPS could be used as a surrogate for OS in patients with advanced non-squamous NSCLC with unknown oncogenic driver mutations and therefore limited options for subsequent chemotherapy. Our findings also suggest that subsequent treatment after disease progression following first-line chemotherapy may greatly influence OS. These results should be validated in other larger populations.

Key words: non-small cell lung cancer, overall survival, post-progression survival, progression-free survival, tumor response

Lung cancer is the most common cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of lung cancers [1]. Overall survival (OS) is considered the most reliable endpoint in cancer studies, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint [2]. This endpoint is precise, easy to measure, and can be documented by the date of death. Surrogate endpoints such as tumor response and progression-free survival (PFS) are also useful endpoints for phase II oncology clinical trials because they can be measured earlier, can be measured more conveniently, and occur more frequently than the main endpoints of interest, which are referred to as the true endpoints.

In view of the growing number of drugs and combinations thereof that are available for the treatment of NSCLC, the effects of first-line chemotherapy on OS might be confounded by subsequent therapies [3]. Indeed, PFS improvements do not necessarily result in an improved OS, as shown by recent randomized trials in patients with NSCLC [4]. In recent years, as for breast, ovarian, and colorectal cancers [5-7], a growing number of active compounds are available for second- or third-line chemotherapy for advanced NSCLC. Although PFS following first-line chemotherapy has not been validated as a surrogate endpoint for OS, post-progression survival (PPS) has been shown to be strongly associated with OS after first-line chemotherapy for advanced NSCLC [8, 9]. PPS has also come to be strongly associated with OS during the last

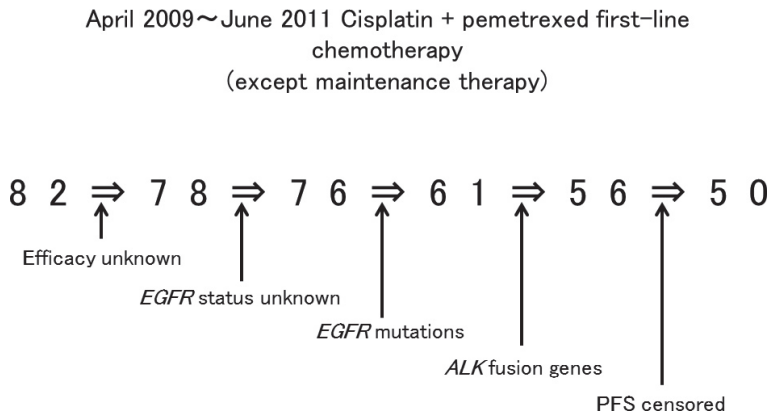

Figure 1. Flow chart showing patient selection.

decade (2002–2012) when molecular targeted agents such as gefitinib and erlotinib were introduced as chemotherapeutic agents for advanced NSCLC [8, 9]. The evaluation of PPS by using a simple method was first reported in 2009 [2]: OS was expressed as the sum of PFS and PPS.

At the individual level, the effect of therapies administered after disease progression on survival is of interest. To date, the validation of surrogate measures for OS after first-line therapy, at the individual level, in patients with advanced NSCLC has not been reported. Further, the surrogate endpoint sometimes does not reflect the primary endpoint. Therefore, examination of whether PFS, PPS, or tumor response could be valid surrogate endpoints for OS after first-line therapy in patients with advanced NSCLC using individual-level data might be of clinical importance.

Platinum-based doublet chemotherapy is the standard of care for advanced NSCLC, based on modest benefits in survival and quality of life as compared with best supportive care only [10-15]. Although many patients initially achieve clinical remission or disease control with first-line chemotherapy, most subsequently experience disease progression and eventually die of advanced NSCLC. We examined first-line cisplatin and pemetrexed combination chemotherapy because this combination is considered standard first-line chemotherapy for advanced NSCLC [15]. Recently, in a phase 3 study of advanced NSCLC, first-line chemotherapy with pemetrexed plus cisplatin was more effective for patients with adenocarcinoma and large cell carcinoma than was gemcitabine/cisplatin (median survival of 11.8 versus 10.4 months, $P = 0.005$) [15]. The median survival time (MST) of patients harboring an *EGFR* mutation treated with gefitinib, platinum, and pemetrexed or docetaxel was reported to be approximately 3 years [16]. However, the MST of patients without an *EGFR* mutation was approximately 1 year. For advanced NSCLC patients without oncogenic driver mutations, such as an *EGFR* mutation, OS is shorter and options for subsequent chemotherapy is currently limited.

In the present study, we analyzed the relationships of PFS, PPS, and tumor response with OS in patients with advanced non-squamous NSCLC at the individual level. The patients evaluated had unknown oncogenic driver mutations, and therefore, options for subsequent-line chemotherapy were limited. We also explored the prognostic value of baseline and tumor characteristics for PPS.

Patients and methods

Patients. Between April 2009 and June 2011, 82 patients with advanced non-squamous NSCLC were treated with cisplatin and pemetrexed as first-line chemotherapy and were enrolled in this study. The tumor response was not evaluated in 4 patients, an unknown *EGFR* mutation status was noted in 2, an *EGFR* mutation was observed in 15, the ALK fusion gene was identified in 5, and PFS data were censored in 6. These 32 patients were excluded from the analyses to unify patient background. Patients receiving maintenance therapy were also not considered. Thus, data from 50 patients were analyzed (Figure 1). The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (#.24-J82-24-1-3).

Patients in this study were treated with cisplatin (75 $mg \cdot m^{-2} day^{-1}$) and pemetrexed (500 $mg \cdot m^{-2} day^{-1}$ for 1 day, followed by a pause of 21 days). This cycle was repeated every 21 days for 6 courses.

The best overall response and maximum tumor shrinkage were recorded as tumor responses. Radiographic tumor responses were evaluated according to the Response Evaluation Criteria In Solid Tumors, ver. 1.1 [17]: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the target lesion diameters with the summed baseline diameters as a reference; progressive disease (PD), at least a 20% increase in the sum of the target lesion diameters with the smallest sum observed during the study serving as reference; and stable disease (SD), insufficient shrinkage to qualify as PR and insufficient expansion to qualify as PD. PFS was calculated from the start of treatment to the date of PD or death from any cause. OS was recorded from the first day of treatment until death or was censored on the

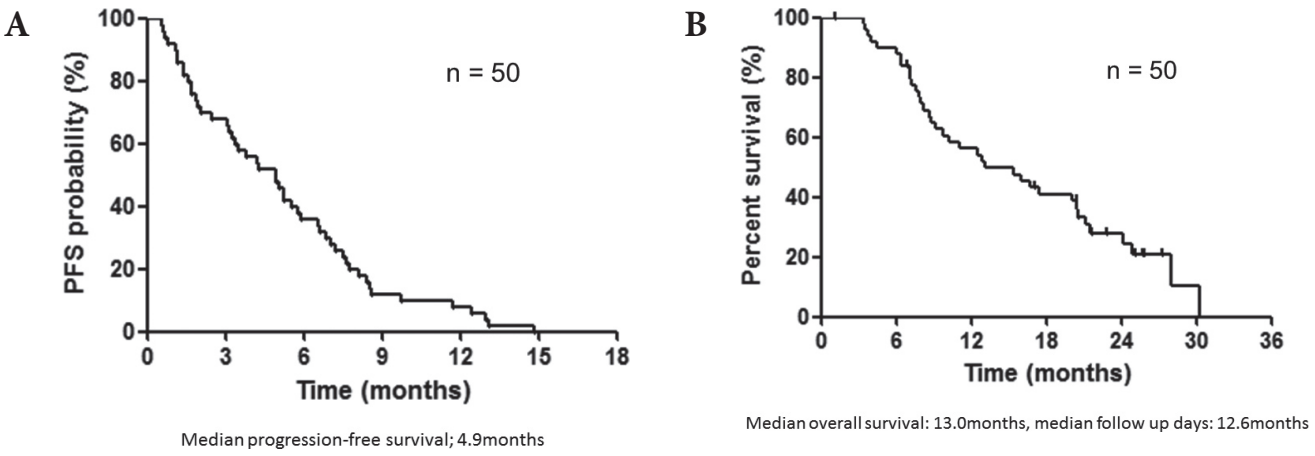

Figure 2. A. Kaplan-Meier plots showing progression-free survival (PFS). B. Kaplan-Meier plots showing overall survival (OS).

date of the last follow-up consultation. PPS was recorded as the time from tumor progression until death or was censored on the date of the last follow-up consultation.

Statistical analysis. To examine whether PFS, PPS, or tumor shrinkage was correlated with OS, we used Spearman rank correlation analysis and linear regression analysis. To explore prognostic factors for PPS, the proportional hazards model with a stepwise regression procedure was applied. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using the model. Because the HR is defined for a 1-unit difference, some factors were converted to an appropriate scale unit. PPS values were compared using the log-rank test. A P value of ≤0.05 was considered significant for all tests. The two-tailed significance level was also set at 0.05. All statistical analyses were performed using JMP version 9.0 for Windows (SAS Institute, Cary, NC, USA).

Table 1. Baseline patient characteristics.

Characteristic	
Gender	
Male/female	37/13
Median age at treatment (years)	64 (40–76)
Performance Status (PS)	
0/1/≧2	19/31/0
Histology	
Adenocarcinoma/others	47/3
Stage	
IIIB/IV	4/46
Number of first-line chemotherapy courses	
1/2/3/4/5/6	5/10/1/22/2/10
Number of regimens after progression following first-line chemotherapy	
0/1/2/3/4/5/6	10/18/11/4/5/1/1
Median (range)	1 (0–6)
Median sum of target lesion diameters [mm] (range)	57 (22–185)

Results

Patient characteristics and treatment efficacy. Of the 50 patients included in the analyses, 37 patients died; the median follow-up time was 12.6 months (range, 1.0–27.9 months). The characteristics of the 50 patients (median age, 64 years; range, 40–76 years) included in the present study are shown in Table 1. Target lesions were not evaluated in one patient.

In the 50 patients, 15, 21, and 14 showed PR, SD, and PD, respectively. The response rate was 30.0% and the disease control rate was 72.0%.

After progressing past first-line chemotherapy, 10 of the 50 patients did not receive post-chemotherapy. The other 40 patients received subsequent chemotherapy after completing their first-line chemotherapy. Among the 50 patients, the median number of follow-up therapeutic regimens was one (range, 0–6 regimens). The chemotherapy regimens employed, after progressing past the first-line chemotherapy regimen, are shown in Table 2. The administration of docetaxel was most common in second-line chemotherapy, and the administration of amrubicin was the most common third-line chemotherapy.

The median PFS and OS were 4.9 months and 13.0 months, respectively (Figures. 2A, B).

Relationship between overall survival and progression-free survival, post-progression survival, and tumor shrinkage. The relationship between OS and PFS, PPS, and tumor shrinkage is shown in Figures 3A, 3B, and 3C, respectively. PPS was strongly associated with OS ($r = 0.89$, $P < 0.05$, $R^2 = 0.79$), based on Spearman's rank correlation coefficient and linear regression, whereas PFS was moderately correlated with OS ($r = 0.67$, $P < 0.05$, $R^2 = 0.39$). Furthermore, tumor

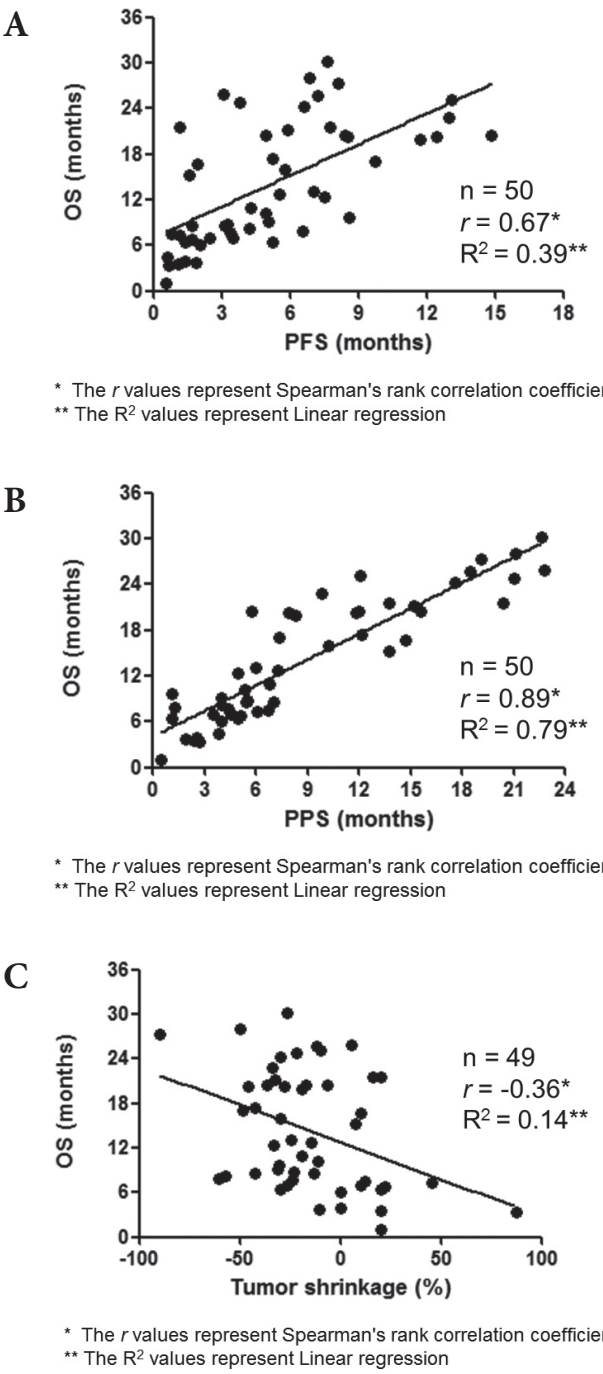

Figure 3. A. Correlation between overall survival and progression-free survival. B. Correlation between overall survival and post-progression survival. C. Correlation between overall survival and tumor shrinkage.

shrinkage was only weakly correlated with OS ($r = 0.36$, $P < 0.05$, $R^2 = 0.14$).

Factors affecting post-progression survival. PPS was strongly associated with OS. Therefore, the association between PPS and various clinical factors was assessed. In the univariate analysis (Table 3), the performance status (PS) at the beginning of first-line treatment, at the end of first-line treatment, and at the beginning of second-line treatment, as well as the best response from the second-line treatment and the number of regimens employed after progression beyond first-line chemotherapy were found to be associated with PPS ($P < 0.05$). Next, a multivariate analysis for PPS was conducted to clarify which clinical factors could affect PPS (Table 4). The PS at the beginning of the second-line treatment, the best response after the second-line treatment (non-PD/PD), and the number of regimens employed after progression following first-line chemotherapy were significantly associated with PPS ($P < 0.05$).

Table 2. The chemotherapy regimens employed after progression following first-line chemotherapy.

	second-line	≧ third-line	Total
Docetaxel	18	8	26
Erlotinib			
Single agent	2	6	8
Erlotinib ± investigational agent	2	2	4
Others			
Single agent	8	23	31
S1	5	6	11
Amrubicin	0	10	10
Others	3	7	10
Platinum combination	10	2	12
Investigational agent	0	2	2

The log-rank tests confirmed that differences in PPS were observed in patients according to their PS at the beginning of second-line treatment, their best response at second-line treatment (non-PD/PD), and the number of regimens employed after progression following first-line chemotherapy. These 3 factors were significantly associated with PPS (log-rank test, $P < 0.05$ (Figures 4A, 4B, and 4C). According to the PS at the beginning of second-line treatment, the PPS for those with PS 0 was 21.8 months, PS 1 was 6.7 months, and PS 2 was 1.3 months, respectively (log-rank test, $P < 0.001$. Figure 4A). Furthermore, patients with non-PD had a median PPS of 15.6 months compared with their counterparts with PD of 4.9 months, respectively, (log-rank, $P < 0.001$; Figure 4B). According to the number of regimens employed after progression following first-line chemotherapy, the PPS for those without additional regimens was 4.4 months; with 1 additional regimen, the PPS was 5.7 months; and with ≧2 regimens, the PPS was 13.7 months, (log-rank test, $P = 0.013$; Figure 4C). These results remained consistent after adjustment in the Cox proportional hazards models (Table 4).

Discussion

We examined the relationships of OS with PFS, PPS, and tumor shrinkage at the individual level. PPS was strongly

Table 3. Univariate Cox regression analysis of baseline patient characteristics.

	Post-progression survival		
Factors	Hazard ratio	95% CI	*P* value
Gender	1.36	0.65–3.09	0.418
Age (years) at the beginning of first-line treatment	1.02	0.94–1.02	0.331
PS at the beginning of first-line treatment	2.03	1.02–4.32	0.042
Histology	0.42	0.14–1.78	0.208
Stage	2.14	0.64–13.2	0.240
Number of courses of first-line treatment administered	0.82	0.65–1.04	0.113
Sum of target lesion diameters	1.00	0.99–1.01	0.216
Best response at first-line treatment			
PR/non-PR	0.87	0.41–1.74	0.716
non-PD/PD	0.63	0.31–1.40	0.249
PS at the end of first-line treatment	2.63	1.46–4.72	0.001
Age at the beginning of second-line treatment	0.97	0.93–1.02	0.344
PS at the beginning of second-line treatment	7.74	2.54–32.1	<0.001
Best response following second-line treatment			
PR/non-PR	0.19	0.03–0.68	0.007
non-PD/PD	0.12	0.04–0.30	<0.001
Number of regimens after progression beyond first-line chemotherapy	0.71	0.53–0.93	0.011

95% CI, 95% confidence interval; PS, performance status; PR, partial response; PD, progressive disease

Table 4. Multivariate Cox regression analysis for performance status (PS) at the beginning of first-line treatment, PS at the beginning of second-line treatment, best response following second-line treatment, and number of regimens employed after progression beyond first-line chemotherapy.

	Post-progression survival		
Factors	Hazard ratio	95% CI	P value
PS at the beginning of first-line treatment	1.68	0.65–4.85	0.28
PS at the beginning of second-line treatment	6.98	1.80–35.9	<0.01
Best response at second-line treatment			
non-PD/PD	0.15	0.05–0.41	<0.01
Number of regimens employed after progression beyond first-line chemotherapy	0.53	0.32–0.82	<0.01

95% CI, 95% confidence interval; PD, progressive disease

associated with OS, whereas PFS and tumor shrinkage were moderately and weakly correlated with OS, respectively. In addition, PS at the beginning of second-line treatment, the best response to second-line treatment (non-PD vs. PD), and the number of regimens employed after progression following first-line chemotherapy, independently affected PPS.

The validity of surrogate endpoints has been previously determined through meta-analyses [18, 19]. In recent years, biostatisticians have proposed a wide variety of measures for validating surrogate endpoints [20, 21]. Although tumor response and PFS are potential surrogate endpoints for OS in extensive-stage small cell lung cancer [22], their validity is controversial in advanced NSCLC [23]. Broglio *et al.* recently focused on PPS, which they termed as survival post progression (defined as OS minus PFS), in a hypothetical clinical trial setting under the assumption that treatment affected PFS but not PPS [2]. Recently, PPS was found to be strongly associated with OS after first-line chemotherapy for advanced NSCLC in a clinical trial-level [8, 9].

Our results do not correspond with some previous results that have indicated that tumor response and PFS are surrogate endpoints for OS in advanced NSCLC [24, 25]. We analyzed our results pertaining to first-line therapy, and they suggested that PFS and tumor response did not adequately reflect OS in such settings. We found that PFS was much shorter than PPS, and thus, PPS was closely related to OS—the relationship was linear (Figures 3A, 3B). The fact that PPS accounted for the most part of OS suggests that the chemotherapy used was too weak for PFS to prolong OS. Thus, in clinical trials with patients expected to have a short PFS after first-line chemotherapy such as patients without driver mutations, as was the case in our study, factors that affect PPS need to be controlled.

According to trial-level data for advanced NSCLC, long PPS was associated with a good PS and the use of first-line

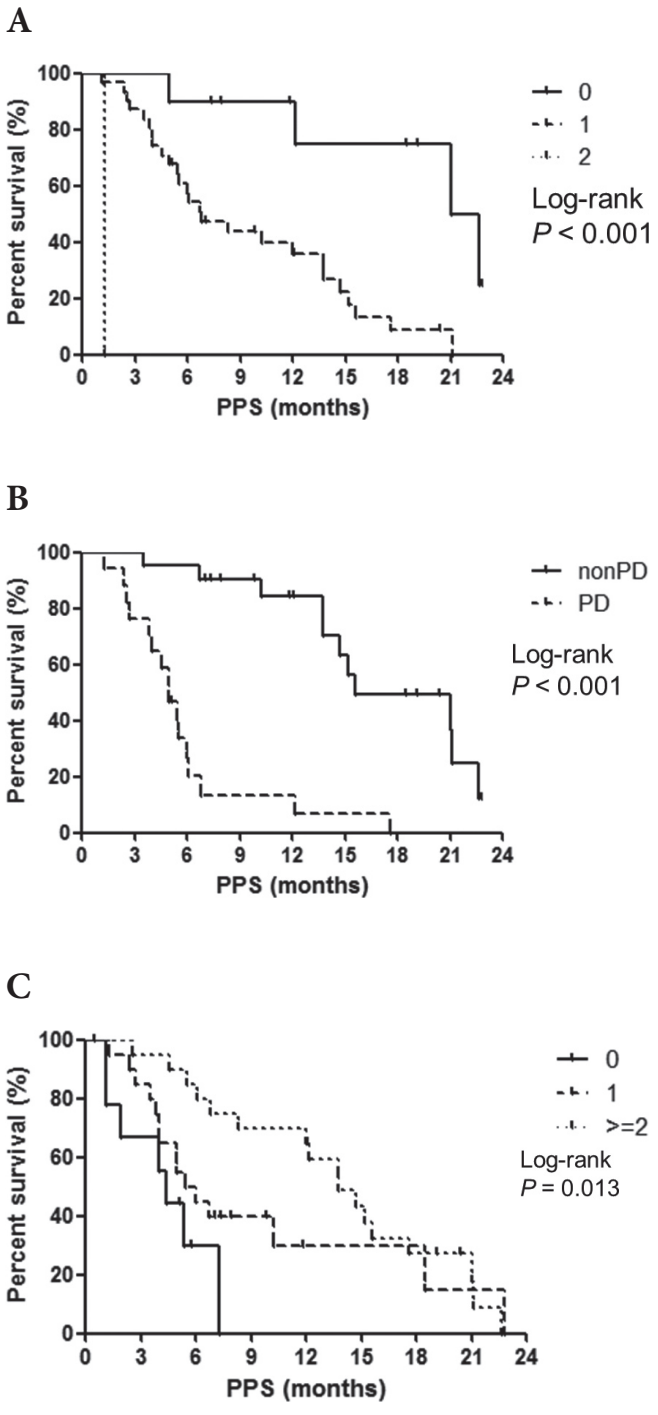

Figure 4. A. Kaplan-Meier plots showing post-progression survival according to performance status (PS) at the beginning of second-line treatment. PS 0, median = 21.8 months; PS 1, median = 6.7 months; PS 2, median = 1.3 months. B. Kaplan-Meier plots showing post-progression survival, according to the best response following second-line treatment. non-progression disease, median = 15.6 months; progression disease, median = 4.9 months. C. Kaplan-Meier plots showing post-progression survival, according to the number of regimens after progression. none, median = 4.4 months; 1 regimen, median = 5.7 months; ≧2 regimens, median = 13.7 months

monotherapy and a molecular targeted agent [8]. However, to date, factors affecting PPS according to individual-level data of patients with advanced NSCLC are unclear. We attempted to explore the prognostic value of baseline factors for PPS. We found that the PS at the beginning of second-line treatment, the best response after second-line treatment, and the number of regimens employed after progression following first-line chemotherapy were strongly related to PPS. Moreover, we confirmed these relationships by log-rank tests. To our knowledge, this study is the first to report on individual-level factors affecting PPS in patients with advanced NSCLC. Our findings suggest that patients with good PS at the beginning of second-line treatment achieve disease stabilization after progression following first-line chemotherapy. These patients are also likely to be able to continue chemotherapy and achieve prolonged PPS, which is associated with OS prolongation. The number of treatment regimens used after progression following first-line chemotherapy is likely the result of the increasing number of active compounds, such as docetaxel, amrubicin, S1, and erlotinib, which are available for second- or third-line chemotherapy for advanced NSCLC. In fact, a number of different compounds were used to treat our patients, as shown in Table 2.

This study has several limitations. First, the sample size was small. However, because the number of advanced non-squamous NSCLC patients treated with first-line cisplatin and pemetrexed, who do not have *EGFR* mutations or *ALK* fusion genes are limited at a single institution, this limitation is difficult to overcome. This is especially true because the purpose of this study was to analyze patients with similar backgrounds. Second, we could not thoroughly evaluate treatments after progression following second-line chemotherapy. However, we consider the results of the present investigation worthwhile because there were few patients receiving third-line or subsequent chemotherapy.

In conclusion, using individual-level data, PFS and tumor response appeared not to be ideal surrogates for OS in patients with advanced non-squamous NSCLC, without an oncogenic driver mutation and therefore limited options for subsequent-line chemotherapy. In these patients, PPS was strongly associated with OS and a PFS advantage was not associated with an OS advantage because of the increasing influence of PPS on OS. In addition, the PS at the beginning of second-line treatment, the best response after second-line treatment (non-PD/PD), and the number of regimens employed after disease progression following first-line chemotherapy were prognostic factors for PPS. In other words, we suggest that the treatment course after progression following first-line chemotherapy greatly influences OS. We believe these results are worth validating with regard to their generalizability to other larger populations.

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