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Predictive Factors for Poor Progression-free Survival in Patients with Non-small Cell Lung Cancer Treated with Nivolumab

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Abstract. *Background: Nivolumab has shown promising effects in patients with non-small-cell lung cancer (NSCLC) as a second- or later-line treatment. This study aimed to identify patients who would not experience any benefit from nivolumab treatment. Materials and Methods: In this study, data for 201 patients treated with nivolumab during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We collected clinical data at the time of nivolumab treatment commencement. We investigated the relationship between progression-free survival (PFS) and patient characteristics. Results: In both univariate and multivariate analysis, performance status (PS) score ≥2, steroid use at baseline and lactate dehydrogenase (LDH) level >240 IU/l were significantly associated with poor PFS (all p<0.05). Conclusion: PS score ≥2, steroid use at baseline and a high LDH level were predictive of poor PFS in patients with NSCLC treated with nivolumab. Careful monitoring is recommended for treating such patients with nivolumab (UMIN-ID: UMIN000025908).*

Treatment options for non-small-cell lung cancer (NSCLC) patients with wild-type epidermal growth factor receptor (*EGFR*) gene status and disease progression after the first cytotoxic chemotherapy course are limited. Docetaxel has been mainly administered as second-line therapy for advanced NSCLC because of its demonstrated efficacy (1, 2).

The program death (PD)-1 receptor is an immune checkpoint inhibitor expressed on activated B- and T-cells that down-regulates excessive immune responses (3, 4). Binding of PD1 to its ligands PDL1 and PDL2 on tumor cells suppresses T-cells through a negative feedback loop, leading to evasion from the immune response (5-8). Nivolumab, a human IgG4 antibody to PD1, disrupts PD1-mediated signaling and may restore antitumor immunity (9-11). Nivolumab has shown promising effects in patients with NSCLC as a second-line or later treatment. In previous phase III studies, progression-free survival (PFS) was 2.3-3.5 months. Moreover, nivolumab treatment resulted in superior overall survival (OS) of 9.2-12.2 months, when compared to docetaxel treatment, particularly in patients with squamous cell carcinoma (12, 13). However, nivolumab does not lead to beneficial effects in 80% of patients. Previous studies have shown that among patients receiving third-line therapy, those with central nervous system metastases, those who had never smoked, those with *EGFR* mutation-positive status, those with anaplastic lymphoma kinase (*ALK*) rearrangement, those aged 75 years or older, and those with a poor performance status (PS) had a worse prognosis when they received nivolumab treatment (12-16). Moreover, the PFS may be shorter in a clinical setting than in a clinical trial owing to the inclusion of random patients, such as those with a poor PS, those receiving steroids, and those with several comorbidities. For treatment effectiveness, it is important to clarify which patients may not experience any benefit from nivolumab treatment. Therefore, in this multicenter retrospective study, we aimed to identify which patients would not be suitable for nivolumab treatment.

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Key Words: Non-small-cell lung cancer, immune checkpoint inhibitor, program death 1, nivolumab, prognosis, progression-free survival.

Materials and Methods

Patients. The data for 204 patients scheduled to receive nivolumab at the National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, and Osaka Prefectural Medical Center for Respiratory and Allergic Diseases from 17 December 2015 to 31 July 2016 were retrospectively reviewed. Three patients died before treatment; therefore, 201 patients were included in the analysis. Written informed consent was obtained for the use of these data. The study protocol was approved by the Institutional Review Board (No. 563; 20 October 2016) of the National Hospital Organization Kinki-chuo Chest Medical Center (Osaka, Japan). The study conformed to the guidelines of the 1964 Declaration of Helsinki and its later amendments. This study was registered at UMIN UMIN-ID: UMIN000025908. All data were examined by outsourcing.

Data collection. We collected clinical data including age, sex, smoking history, PS score, body mass index (BMI), histological type, *EGFR* mutation status, number of previous treatments, steroid use, and laboratory data [lactate dehydrogenase (LDH) and C-reactive protein (CRP)] at the time of nivolumab treatment commencement. Clinical responses were defined according to Response Evaluation Criteria in Solid Tumors 1.1 (17). PFS was estimated as the duration between nivolumab treatment initiation and documented disease progression or death from any cause. We investigated the relationship between PFS and patient characteristics. Patients were followed-up for disease status until September 2016.

Statistical analyses. Statistical analyses were performed using the JMP statistical software program (11th version; SAS Institute Inc., Cary, NC, USA) to compare clinical outcomes according to patient characteristics. Survival curves were estimated using the Kaplan–Meier method, and the differences between the two groups were compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics. The median age at the time of nivolumab treatment was 68 years, 135 patients were male, 157 patients had a history of smoking, 153 patients had a PS score of 0-1, median BMI was 21.42 kg/m^2, 42 patients had squamous-cell carcinoma, 142 patients had adenocarcinoma, 37 patients had *EGFR* mutations, 78 patients received 3 or more treatments before nivolumab, and 23 patients received steroids (Table I).

Survival analysis. The median PFS was 2.9 months (Figure 1), the overall response rate was 15.9%, disease control rate was 51.7%, and progressive disease rate was 44.8%.

Predictive factors for PFS. n the univariate analysis, a PS score of 2 or more (p=0.010), steroid use at baseline (p<0.001), and LDH level >240 IU/l (p=0.003) were significantly associated with poor PFS (Table II). In the multivariate analysis, these three factors remained significantly associated with poor PFS (Table III). A multivariate analysis with patients grouped according to PS, PS score ≤2 and PS ≥3, showed that a PS score of 3 or more was significantly related to poor PFS (p<0.001) (Table IV). However, only 15 patients had a PS score of 3 or more. Therefore, we regrouped the patients into those with a PS score of ≤1 and ≥2.

Table I. *Patient baseline characteristics*.

Characteristic	Patients (n=201)
Median age (range), years	68 (27-87)
Gender: Male/female	135/66
Smoking history: Yes/no	157/44
Performance status score: 0/1/2/3/4	32/121/33/12/3
Median body mass index (range), kg/m^2	21.4 (12.9-37.8)
Histological types: SCC/ADC/other	42/142/17
EGFR-mutation: Positive/negative	37/164
Previous treatment: 0/1/2/≥3	1/78/44/78
Steroid use: Yes/no	23/178

SCC, Squamous cell carcinoma; ADC, adenocarcinoma; EGFR, epidermal growth factor receptor.

The reasons for steroid use included fatigue (n=6), brain metastasis (n=5), side effects induced by previous treatment (n=2), pain control (n=2), rheumatoid arthritis (n=2), anorexia (n=2), tumor-related fever (n=1), respiratory failure due to tumor progression (n=1), carcinomatous meningitis (n=1), and carcinomatous lymphangiomatosis (n=1). In addition, the median dose of steroids received (converted to prednisolone equivalents) was 6.25 mg (range=1.56-12.50 mg).

In the log-rank test, PS score of 2 or more (1.5 *vs*. 3.3 months; p=0.006), steroid use at baseline (1.2 *vs*. 3.2 months; p<0.001) and LDH level >240 IU/l (1.5 *vs*. 3.7 months; p=0.002) were significantly correlated with poor PFS (Figure 2).

Discussion

In the univariate and multivariate analysis, PS score of 2 or more, steroid use at baseline, and LDH level >240 IU/l were found to be significantly associated with poor PFS for patients treated with nivolumab. In addition, a multivariate analysis of patients grouped according to PS showed that a PS score of 3 or more was significantly related to poor PFS. To the best of our knowledge, this is the first study to examine the predictive factors of PFS during nivolumab treatment using a multivariate analysis.

In previous phase III studies, nivolumab led to a PFS of 2.3-3.5 months with an objective response rate of 19-20% (12, 13). However, in our study, the median PFS was 2.9 months, objective response rate 15.9%, and PD rate 44.8%.

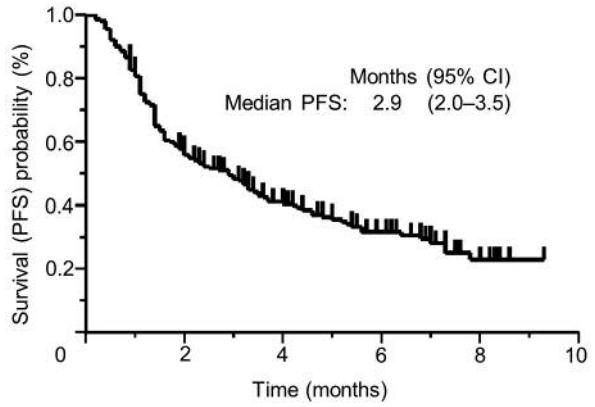

Figure 1. *Progression-free survival (PFS) curve. Kaplan–Meier curves for patients with non-small-cell lung cancer treated with nivolumab (n=201). CI: Confidence interval.*

Table II. *Univariate Cox proportional hazards model analysis of factors associated with progression-free survival.*

Factor	HR	95% CI	*p*-Value
Female gender	1.28	0.89-1.81	0.179
Age <70 years	1.13	0.80-1.60	0.487
Squamous cell carcinoma	1.41	0.92-2.08	0.109
Never smoker	1.27	0.85-1.85	0.245
EGFR mutation positivity	1.39	0.91-2.06	0.123
Previous treatments, ≥3	1.09	0.77-1.53	0.638
PS score ≥2	1.68	1.13-2.44	0.010
Steroid use	2.49	1.52-3.90	<0.001
BMI ≤20 kg/m^2	1.38	0.97-1.94	0.077
CRP >0.3 mg/dl	1.40	0.98-2.04	0.067
LDH >240 IU/l	1.69	1.19-2.39	0.003

HR, Hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; PS, performance status; BMI, body mass index; CRP, C-reactive protein; LDH, lactate dehydrogenase.

This difference may be attributable to the selection of random patients in a clinical setting. In clinical trials, patients with unfavorable conditions are excluded. However, because we encounter patients with various conditions in clinical practice, it is important to identify those unsuitable for nivolumab treatment.

Steroid use at the time of nivolumab treatment commencement was significantly associated with poor PFS. Horvat *et al*. reported that for patients with melanoma, steroid use for treatment of side-effects due to ipilimumab did not influence treatment outcomes (18). Moreover, Freeman-Keller *et al*. reported that among patients with metastatic melanoma treated with nivolumab, the overall survival was significantly longer among those who received systemic steroids than those who did not (19). However, there was no evidence of a relationship between steroid use at baseline and the effect of nivolumab. Upon acceleration of the immune response, steroids may not negatively influence the effects of nivolumab. Nevertheless, because they are known to induce apoptosis of T-lymphocytes (20), steroids may impede the acceleration of the immune response. Furthermore, among patients using steroids at the time of nivolumab treatment, 12 had a PS score of 0-1 and 11 had a PS score of 2-4. Therefore, the poor PS might have resulted in the poor PFS. However, further studies are needed to confirm this relationship.

A high serum LDH level was also significantly associated with poor PFS. In previous studies, the serum LDH level was significantly related to the extent of the tumor and poor prognosis in patients with NSCLC (21-24). Increased LDH activity results in lactic acid production and acidification of the extracellular water space, which is a very common feature in cancer. Acidic extracellular pH has been shown to activate gelatinase activity and the production of cathepsin D, which contribute to an increased invasive ability of cancer cells. Activation of macrophage-mediated angiogenesis by lactate may also facilitate metastasis (21). Furthermore, Diem *et al*. reported that among patients with advanced/metastatic melanoma treated with nivolumab or pembrolizumab, after a median follow-up of 9 months those with an elevated baseline LDH level had a significantly

Table III. *Multivariate Cox proportional hazards model analysis of factors associated with progression-free survival.*

Factor	HR	95% CI	*p*-Value
PS score ≥2	1.57	1.06-2.29	0.027
Steroid use	2.37	1.44-3.74	0.001
LDH >240 IU/l	1.63	1.15-2.31	0.007

HR, Hazard ratio; CI, confidence interval; PS, performance status; LDH, lactate dehydrogenase.

Table IV. *Multivariate Cox proportional hazards model analysis of factors associated with progression-free survival after grouping patients according to performance status (PS).*

Factor	HR	95% CI	*p*-Value
PS ≥3	3.18	1.70–5.53	<0.001
Steroid use	2.17	1.30-3.45	0.004
LDH >240 IU/l	1.66	1.17-2.35	0.005

HR, Hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase.

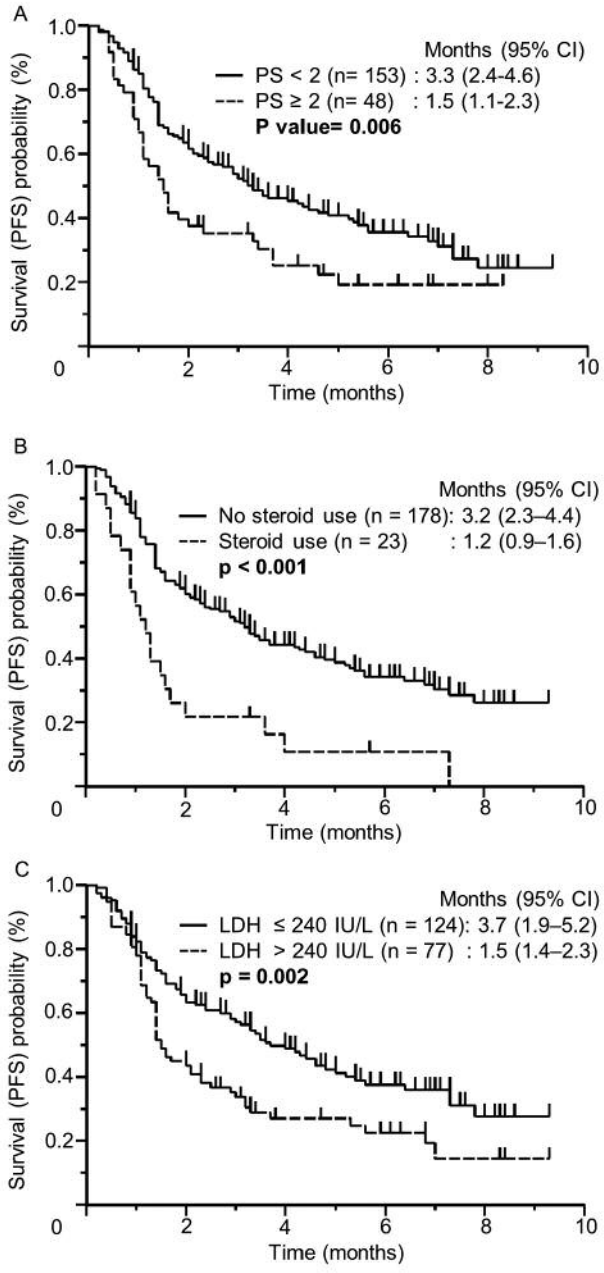

Figure 2. *Progression-free survival (PFS) curves. Kaplan–Meier curves for patients with non-small-cell lung cancer treated with nivolumab (n=201) stratified by performance status (PS) score cut-off value of 1 (A), steroid use at the start of nivolumab treatment (B) and a lactate dehydrogenase (LDH) level cut-off value of 240 IU/l (C). CI: Confidence interval.*

shorter overall survival than those with normal LDH level (25). Therefore, a high LDH level may be related not only to the prognosis of NSCLC but also to the efficacy of immune checkpoint inhibitors.

In a previous phase III trial comparing patients with non-squamous cell NSCLC treated with nivolumab and docetaxel, patients who were receiving third-line therapy, those who lived in the geographic region that included South America, Asia, and Australia, those with central nervous system metastases, those who had never smoked, and those with an *EGFR* mutation-positive status had a favorable overall survival with docetaxel treatment (12). Furthermore, comparing patients with squamous-cell NSCLC treated with nivolumab and docetaxel, patients in Argentina, Australia, Chile, Mexico, and Peru and those who were 75 years of age or older had a favorable overall survival with docetaxel treatment (13). In our study, the univariate analysis showed that a never-smoker status, *EGFR* mutation positivity and age were not predictive factors for prognosis. However, we did not examine the metastatic status.

In the two phase III trials mentioned above, high tumor PDL1 protein expression was associated with better outcomes (12, 13). Nevertheless, even in the absence of PDL1 expression, some patients showed a good response to the treatment. Therefore, low PDL1 expression should not be a reason for not prescribing nivolumab.

Kanai *et al*. reported that in patients with decreased PS or central nervous system metastases, severe events (mostly neurologic symptoms) frequently led to the discontinuation of nivolumab treatment in the early phase (14). Our sample size was much larger than that in this previous study, and our findings confirm their results. Gainor *et al*. reported that *EGFR* mutations or *ALK* rearrangements are associated with poor prognosis (15). Moreover, Lee *et al*. reported that in *EGFR*-mutant advanced NSCLC, immune checkpoint inhibitors do not improve overall survival to an extent greater than that achieved with docetaxel (16). In our study, *EGFR* mutation positivity was not a factor predictive of poor PFS in the univariate analysis. In addition, in our study, only one patient had an *ALK* rearrangement; therefore, *ALK* rearrangement was not further examined. However, it should be noted that the studies mentioned above did not conduct multivariate analysis.

The limitations of this study are its retrospective nature and relatively small sample size. Further studies are needed to validate our findings.

In summary, PS score of 2 or more, steroid use at baseline and a high LDH level were predictive of a poor PFS in patients with NSCLC treated with nivolumab. Therefore, careful monitoring is recommended for treating such patients with nivolumab.

Conflicts of Interest

Dr. Y. Taniguchi, Dr. A. Tamiya, Dr. S. Isa, Dr. K. Nakahama, Dr. T. Shiroyama, Dr. H. Suzuki, Dr. T. Inoue, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura and Dr. S. Atagi report grants from Ono Pharmaceutical and Bristol-Myers Squibb, Dr. Y. Taniguchi, Dr. A.

Tamiya, Dr. T. Shiroyama, Dr. H. Suzuki, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura and Dr. S. Atagi report personal fees from Ono Pharmaceutical and Dr. Y. Taniguchi, Dr. A. Tamiya, Dr. M. Tamiya, Dr. T. Hirashima, Dr. F. Imamura and Dr. S. Atagi report personal fees from Bristol-Myers Squibb during the conduct of the study. Dr. Y. Taniguchi reports personal fees from Chugai Pharmaceutical outside the submitted work. Dr. A. Tamiya reports personal fees from Chugai Pharmaceutical, AstraZeneka, Eli Lilly and Boehringer Ingelheim outside the submitted work. Dr. K. Okishio reports personal fees from Ono Pharmaceutical outside the submitted work. Dr. T. Shiroyama reports personal fees from Taiho Pharmaceutical, Boehringer Ingelheim and AstraZeneca outside the submitted work. Dr. H. Suzuki reports personal fees from Taiho Pharmacetical, Boehringer Ingelheim, Pfizer and Eli-Lilly outside the submitted work. Dr. M. Tamiya reports personal fees from Chugai Pharmaceutical, Pfizer, AstraZeneca, Taiho Pharmaceutical, Eli Lilly, Asahi Kasei Pharmaceutical, Daichi Sankyo CO. LTD. Alere Medical and Boehringer Ingelheim outside the submitted work. Dr. K. Nishino reports personal fees from Chyugai, Boehringer Ingelheim, Eli Lilly and AstraZeneca outside the submitted work. Dr. T. Kumagai reports personal fees from Ono Pharmaceutical, Astra Zeneca and Boehringer Ingelheim outside the submitted work. Dr. T. Hirashima reports grants and personal fees from MSD Oncology, Lilly Japan, AstraZeneca, Chugai Pharma and Boehringer Ingelheim, grants from Eisai, Daiichi Sankyo, Merck Serono, Taiho Pharmaceutical, Kyowa Hakko Kirin and Takeda, and personal fees from Bayer outside the submitted work. Dr. F. Imamura reports personal fees from Pfizer Inc, AstraZeneca K. K., Novartis Pharma K. K., Kyowa Hakko Kirin Co. Ltd., Boehinger Ingelheim GmbH, Taiho Pharmaceutical Co. Ltd., Eli Lilly Japan K. K., Chugai Pharceutical Co. Ltd., outside the submitted work. Dr. S. Atagi reports grants from Pfizer, Chugai Pharmaceutical, AstraZeneca, MSD, Taiho Pharmaceutical, Yakult Pharmaceutical Industry, Eli Lilly and Boehringer Ingelheim and personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, Eli Lilly and Boehringer Ingelheim outside the submitted work.

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