

Relationship Between TTF-1 Expression and PFS of Pemetrexed-containing Chemotherapy in Non-squamous-NSCLC Patients With and Without Driver Genes

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Abstract. *Background/Aim:* We performed a retrospective study to clarify whether the presence or absence of driver genes affects the relationship between thyroid transcription factor-1 (TTF-1) expression and response to pemetrexed (PEM) in non-squamous non-small cell lung cancer (non-sq-NSCLC) patients. *Patients and Methods:* We reviewed the medical charts of patients treated with PEM-containing chemotherapy during the period from February 2016 to February 2022 at Mito Medical Center-University of Tsukuba, Ryugasaki Saiseikai General Hospital, and University of Tsukuba Hospital. *Results:* During the period of the study, 185 driver gene-negative patients, and 65 driver gene-positive patients were evaluated. Among the 165 driver gene-negative patients, progression free survival (PFS) of TTF-1-expressing patients treated with PEM-containing chemotherapy was significantly longer compared to that of TTF-1-negative patients. In the analysis of 65 driver gene-positive patients, the PFS of TTF-1-positive patients treated with PEM-containing chemotherapy did not

differ significantly from that of TTF-1-negative patients. There was no significant difference in PFS between driver gene-negative and driver gene-positive patients treated with PEM-containing chemotherapy. Comparison between four groups defined according to the presence of driver gene and TTF-1 expression indicated shorter PFS only in 'driver gene-negative and TTF-1-negative' patients. *Conclusion:* In driver gene-positive non-sq NSCLC patients, expression of TTF does not affect the survival outcome of PEM-containing-chemotherapy. In other words, in these patients, second-line or later-line PEM-containing chemotherapy after development of resistance for specific-tyrosine kinase inhibitor could be expected to have the same level of efficacy as first-line PEM containing chemotherapy in driver gene-negative, TTF-1-positive non-sq NSCLC patients.

Thyroid transcription factor-1 (TTF-1) is expressed in thyroid follicle, parathyroid gland, alveolar epithelium, and diencephalon, and participates in the differentiation, development, and functional maintenance of these organs (1-3). A number of studies have shown that TTF-1 expression is associated with improved survival in patients with advanced non-squamous non-small cell lung cancer (non-sq-NSCLC) (4-6). More interesting, expression of TTF-1 has been shown to be associated with the efficacy of several antitumor drugs and progression-free survival (PFS) (7-15). Of note, non-sq-NSCLC patients with TTF-1 expression have been shown to have a better prognosis than those without expression, responding to pemetrexed (PEM)-containing chemotherapy (7-15). Due to its high response rate and low incidence of serious side effects, PEM has become one of the essential antineoplastic agents for non-sq-NSCLC in routine clinical practice (7-15). Some of these previous studies examined the correlation between the expression of TTF-1 and PFS of patients treated with PEM-

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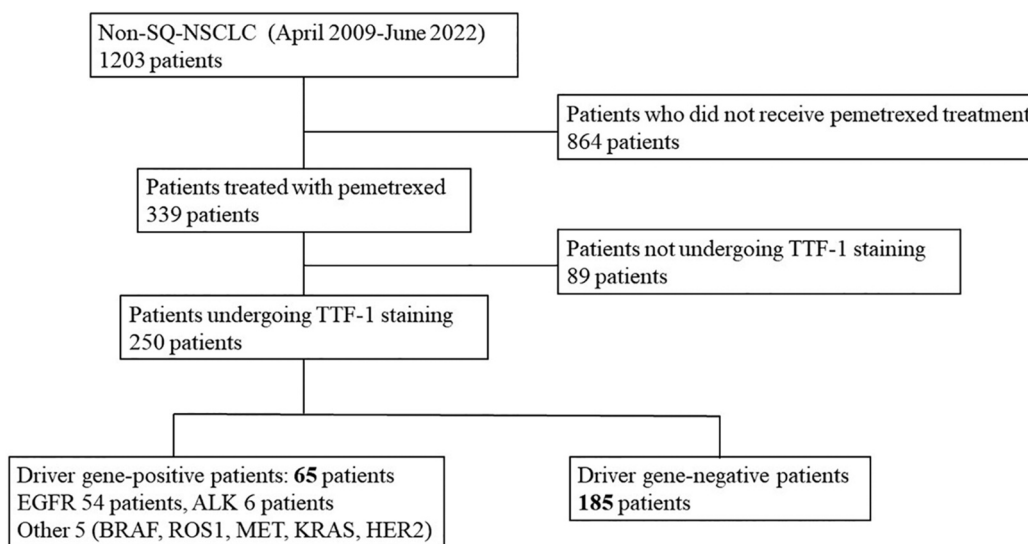


Figure 1. Flowchart of patient selection.

containing chemotherapy including non-sq NSCLC patients with driver mutations, such as epidermal growth factor receptor (*EGFR*) mutation (8, 10-12, 14, 15). However, none of them analyzed the association between TTF-1 expression and PEM response considering the presence or absence of the driver gene. Driver gene-positive NSCLC, such as those carrying an *EGFR* mutation or an *ALK* rearrangement, can be treated with specific responsive tyrosine kinase inhibitors (TKIs). In such driver gene-positive patients, TKIs are prescribed as the first-line therapy. Therefore, the treatment sequence for these patients is clearly different from that for patients with driver gene-negative NSCLC. It is also unclear how the presence or absence of the driver gene is related to response to PEM-containing chemotherapy.

Therefore, we conducted this study to clarify whether the presence or absence of the driver gene affects the relationship between TTF-1 expression and response to PEM in non-sq-NSCLC patients.

Patients and Methods

This study examined the medical records of all patients diagnosed with NSCLC between April 2009 and June 2022 at three tertiary hospitals: Mito Medical Center, University of Tsukuba, Ryugasaki Saiseikai General Hospital, and University of Tsukuba Hospital. NSCLC was pathologically diagnosed using the World Health Organization classification with tumor node metastasis staging (TNM Classification, eighth Edition) (16). Staging was performed from computed tomography/magnetic resonance imaging of the head, ultrasonography/computed tomography of the abdomen, and bone scans. Patient demographics including age, sex, histopathology, disease stage and survival were extracted from their medical records. We confirmed the presence or absence of driver

genes. The study included patients with non-sq-NSCLC receiving first-line or later lines of PEM-containing chemotherapy.

Expression of TTF-1 was assessed by immunohistochemical staining using a rabbit monoclonal antibody (1:250; Abcam, Cambridge, UK). We evaluated the degree of positivity as follows: negative (-, 0%); very focally positive (+, <25% in hot spots); focally positive (++, <50% in hot spots); diffusely positive (+++, >50% and a uniform pattern). In this study, only 'diffusely positive' were treated as TTF-1-positive.

Statistical analysis. Nominal variables were compared using a chi-squared test and values with an unknown population variance were compared using a nonparametric Mann-Whitney test. PFS was defined as the period from randomization to disease progression or death from any cause. PFS was calculated with a Kaplan-Meier analysis and compared using a log-rank test. Cox proportional hazards modeling with the forward-backward stepwise method was used to identify the independent variables to be included in the final model, with PFS as the dependent variable. Multivariable analyses included only variables with a *p*-value of less than 0.1 in univariate analysis. All statistical analyses were conducted using SPSS version 23 (IBM Corporation, Armonk, NY, USA). A *p*-value of less than 0.05 was considered significant.

Ethics. This study complied with the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent to participate in a non-interventional retrospective study was obtained from each patient. The Mito Medical Center-University of Tsukuba Hospital Ethics Committee approved the examination of medical records for the purpose of this study.

Results

Clinicopathological features of the patients. Figure 1 shows the study flow chart. During the study period, 1,203 non-sq-NSCLC patients were diagnosed. Among them, 339 patients

Table I. Background of clinical features in non-squamous non-small cell lung cancer (NSCLC) patients by thyroid transcription factor 1 (TTF-1) expression.

	TTF-1 positive	TTF-1 negative	p-Value
Driver gene negative patients			
Number of patients	98	87	
Sex M:F	70:28	72:15	0.082
Age, median (range) years	68 (42-85)	67 (42-81)	0.490
Pathology, adenocarcinoma: others	96:2	85:2	0.999
Stage, IIIA-C:IVA-B	25:73	17:70	0.382
Platinum, containing:in-containing	81:17	76:11	0.537
Driver gene positive patients			
Number of patients	53	12	
Sex M:F	20:33	4:8	0.999
Age, median (range) years	68 (29-86)	67 (58-80)	0.261
Pathology, adenocarcinoma: others	53:0	12:0	0.999
Stage, IIIA-C:IVA-B	9:44	0:12	0.191
Platinum, containing:in-containing	41:12	7:5	0.273
EGFR positive patients			
Number of patients	42	12	
Sex M:F	14:28	4:8	0.999
Age, median (range) years	69 (43-86)	67 (58 - 80)	0.876
Pathology, adenocarcinoma: others	42:0	12:0	0.999
Stage, IIIA-C:IVA-B	4: 38	0:12	0.564
Platinum, containing:in-containing	30:12	7:5	0.486

EGFR: Epidermal growth factor receptor.

were treated with PEM-containing chemotherapy. Of these, 250 patients underwent TTF-1 immunostaining before treatment. Of the 250 patients, 185 were negative for any driver gene, and 65 were positive for a driver gene (54 *EGFR* gene positive, 11 other driver gene positive). Table I shows the clinicopathological features of TTF-1-positive and -negative driver gene-negative patients. There were 185 driver gene-negative patients, which were treated with PEM-containing chemotherapy. Among the 185 driver gene-negative patients with non-sq NSCLC, 98 (53.0%) were TTF-1 positive. Fifty-three (81.5%) of 65 driver gene-positive patients were TTF-1 positive: 42 (77.8%) of 54 *EGFR*-positive patients and all six patients carrying the *ALK* rearrangement were TTF-1 positive.

In this study, we designated 'driver gene- negative-TTF-1 positive patient group', 'driver gene- negative-TTF-1 negative patient group', 'driver gene- positive-TTF-1 positive patient group', and 'driver gene- positive-TTF-1 negative patient group' as Group A, Group B, Group C, and Group D, respectively.

Comparison of PFS between driver gene negative patients with or without TTF-1. We first compared the clinicopathological features of Group A and Group B patients. As shown in Table I there was no statistically significant difference between them, so we compared PFS of these groups. Figure 2A shows the Kaplan-Meier curves of

these two groups of patients. PFS of Group A patients was significantly longer than that of Group B patients ($p=0.001$) (median PFS: 9.0 and 4.0 months). In the uni- and multivariate analyses, TTF-1 positivity was confirmed to be a significant favorable factor in patients with driver gene-negative non-sq NSCLC (Table II).

Comparison of PFS between driver gene- positive patients with or without TTF-1. Table II shows the clinicopathological features of Group C and Group D patients. We confirmed that there was no significant difference in the features of these patients, and then compared PFS between driver gene positive patients with or without TTF-1. As shown in Figure 2B, there was no statistically significant difference in PFS between Group C and Group D patients ($p=0.2805$) (median PFS: 7.0 and 5.0 months). In 54 *EGFR*-positive patients, there was no statistically significant difference in PFS between TTF-1-positive and -negative patients ($p=0.6139$) (median PFS: 5.0 and 4.5 months). In univariate analyses, none of the factors favored PFS in patients with driver gene-positive non-sq NSCLC (Table II).

Comparison of PFS between driver gene- positive and negative patients with or without TTF-1. Table III shows the clinicopathological features of driver gene-negative (Group A and B) and driver gene-positive patients (Group

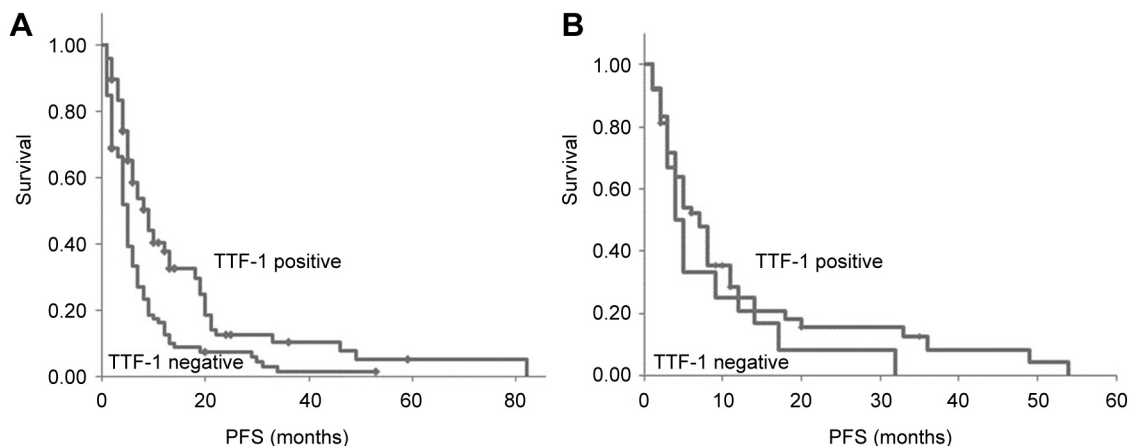


Figure 2. Kaplan-Meier curves of group A and group B patients. Progression-free survival (PFS) of Group A patients was significantly longer than that of Group B patients ($p=0.001$) (median PFS: 9.0 and 4.0 months) (A). Kaplan-Meier curves of PFS in driver gene-positive patients with or without TTF-1. There was no statistically significant difference in PFS between Group C and Group D patients ($p=0.2805$) (B).

Table II. Uni- and multivariate analysis of progression-free survival in non-squamous non-small cell lung cancer (NSCLC) patients with or without driver gene.

	Univariate analysis (p -Value)	Multivariate analysis		
		Hazard ratio	95%CI	p -Value
Patients without driver gene				
Age, less than 65 years	0.800			
Sex, female	0.163			
Stage, IIIA-C	0.920			
Pathology, adenocarcinoma	0.741			
Platinum-containing chemotherapy	0.034	0.446	0.99-2.44	0.050
Expression of TTF-1	0.001	0.659	1.40-2.67	0.001
Patients with driver gene				
Age, less than 65 years	0.175			
Sex, female	0.342			
Stage, IIIA-C	0.124			
Platinum-containing chemotherapy	0.787			
Expression of TTF-1	0.281			

TTF-1: Thyroid transcription factor-1.

C and D). There was no significant difference in the features of these patients except for sex and TTF-1. As ‘sex was not a factor affecting PFS in neither the driver gene-negative group nor the driver gene-positive group (Table II), we compared PFS of driver gene-negative patients with that of driver gene-positive patients. As shown in Figure 3A, there was no significant difference between these two groups ($p=0.9955$). No significant difference in PFS was observed between Groups A, B and C ($p=0.1185$). However, a statistically significant difference in PFS was confirmed between ‘Group A+Group B+Group C’ and Group D ($p=0.001$) (Figure 3B).

Discussion

In this study, the following four results were obtained. First, in 165 driver gene-negative patients, the PFS of TTF-1-expressing patients treated with PEM-containing chemotherapy was significantly longer than that of TTF-1-negative patients, as observed in previous reports (7-15). In uni- and multivariate analysis, the expression of TTF-1 was confirmed as a significant favorable factor for PFS of patients treated with PEM-containing chemotherapy. Second, however, in 65 driver gene-positive patients, PFS of those treated with PEM-containing chemotherapy was not

Table III. Background of clinical features in non-squamous non-small cell lung cancer (NSCLC) patients by thyroid transcription factor-1 (TTF-1) expression.

	Patients		p-Value
	Driver gene negative	Driver gene positive	
Number of patients	185	65	
Sex, M:F	142:43	24:41	0.001
Age, median (range), years	68 (42-85)	68 (29-86)	0.491
Pathology, adenocarcinoma:others	181:4	65:0	0.575
Stage, IIIA-C:IVA-B	42:143	9: 56	0.153
Platinum, containing:incontaining	157:28	48:17	0.060
Bevacizumab, containing:incontaining	74:111	34:31	0.109
ICI, containing:incontaining	32:153	8:57	0.331
TTF-1, positive:negative	98:87	53:12	0.001

ICI: Immune checkpoint inhibitor.

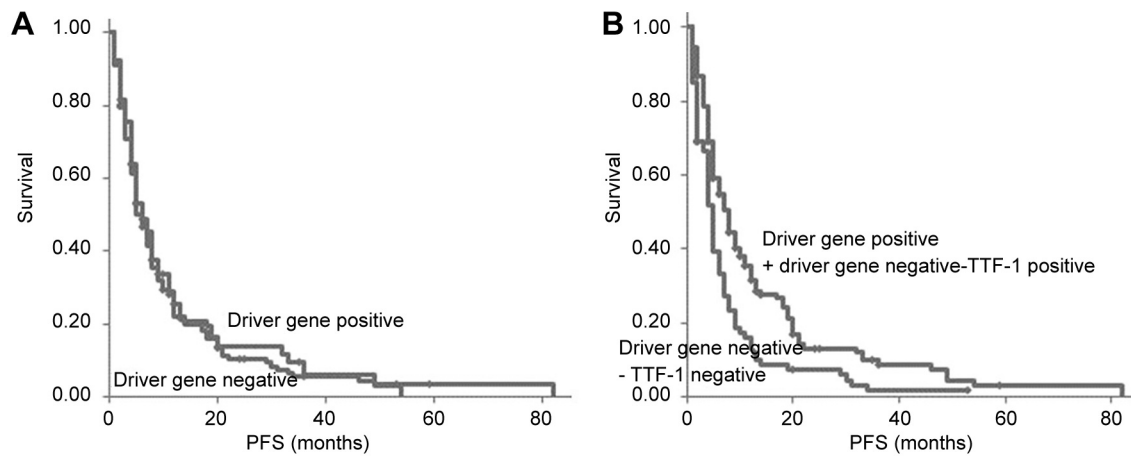


Figure 3. Kaplan-Meier curves of progression-free survival (PFS) in driver-gene negative (group A and group B patients) and driver-gene positive patients (group C and group D patients). There was no significant difference between these two groups ($p=0.9955$) (A). Kaplan-Meier curves of PFS between 'Group A+Group B+Group C' and Group D. There was no statistically significant difference between them ($p=0.001$) (median PFS: 8.0 and 4.0 months) (B).

significantly different from that of TTF-1-negative patients. In 54 *EGFR*-positive patients, the PFS of TTF-1-positive patients treated with PEM-containing chemotherapy was not significantly different from that of TTF-1-negative patients. Third, there was no significant difference in PFS following treatment with PEM-containing chemotherapy between driver gene-negative and driver gene-positive patients. Fourth, the comparison of PFS of patients treated with PEM-containing chemotherapy and grouped according to the presence of driver gene and expression of TTF-1 indicated that PFS was shorter in 'driver gene-negative and TTF-1-negative' patients.

Table IV shows the driver gene and positivity for TTF-1 in previous studies (8, 10, 11, 13, 14, 17-27). The positivity rates varied since the TTF-1 antibody used and the threshold for

positive staining were different in each study, but the positive rate in driver gene-negative patients is generally lower than that in driver gene-positive patients (8, 10, 11, 13, 14, 17-27). This result is consistent with our present study. Regarding driver gene-positive patients, the TTF-1 expression was evaluated only in patients with *EGFR* mutation and those carrying the *ALK* rearrangement as shown in Table IV. To the best of our knowledge, there is no study on TTF-1 expression in patients with other driver genes than *EGFR* mutation and *ALK* rearrangement. Some studies have investigated the relationship between TTF-1 expression and PEM-containing chemotherapy in driver gene-negative patients, but no study examined this relationship in driver gene-positive patients.

In our analysis of 65 driver gene-positive patients (54 of whom were *EGFR* mutation-positive), no significant

Table IV. Driver gene and positivity of thyroid transcription factor-1 (TTF-1) in previous studies.

First author	Year of publication	Journal name	Number of TTF-1 positive patients/all patients evaluated TTF-1 (%)			PFS in PEM chemotherapy	
			Driver gene negative	EGFR mutant	ALK rearrangement	Driver gene negative	Driver gene positive
Sun	2012	J Thorac Oncol	74/109 (69.2)	77/83 (92.8)	-	Not evaluated	Not evaluated
Chung	2012	Chest	169/205 (82.4%)	274/291 (94.2%)	-	Not evaluated	Not evaluated
Vallee	2013	Int J Oncol	675/890 (77.8%)	145/148 (98.0%)	-	Not evaluated	Not evaluated
Gahr	2013	Br J Cancer	526/746 (70.5%)	101/108(93.5%)	-	Not evaluated	Not evaluated
Liu	2014	Pathol Res Pract	59/74 (79.7%)	63/65 (96.9%)	-	Evaluated	Not evaluated
Warth	2014	Eur Respir J	360/412 (87.4%)	56/65 (86.2%)	6/6 (100%)	Not evaluated	Not evaluated
Shanzhi	2014	PLoS One.	375/402 (93.3%)	261/262 (99.6%)	-	Not evaluated	Not evaluated
Somaiah	2014	Oncoscience	49/77 (63.6%)	222/224 (99.1%)	-	Not evaluated	Not evaluated
Elsamany	2015	Asian Pac J Cancer Prev	50/59 (84.7%)	20/21 (95.2%)	-	Evaluated	Not evaluated
Zhao	2015	Onco Targets Ther	80/111 (72.1%)	83/89 (93.3%)	-	Not evaluated	Not evaluated
Zhang	2015	J Thorac Oncol	200/256 (78.1%)	552/602 (91.7%)	37/42 (88.1%)	Not evaluated	Not evaluated
Udupa	2015	Indian J Cancer	35/51 (68.6%)	33/34 (97.1%)	-	Not evaluated	Not evaluated
Schilsky	2017	Lung Cancer	383/479 (80.0%)	92/98 (93.9%)	9/10 (90%)	Evaluated	Not evaluated
Piljić Burazer	2017	Med Sci Monit	102/134 (76.1%)	11/14 (78.6%)	4/6 (66.7%)	Evaluated	Not evaluated
Takeuchi	2018	Anticancer Res	67/92 (72.8%)	25/26 (96.2%)	3/3 (100%)	Evaluated	Not evaluated
Park	2019	BMC Cancer	60/89 (67.4%)	79/84 (94.0%)	-	Not evaluated	Not evaluated
Nakra	2021	J Pathol Transl Med	456/640 (71.3%)	242/269 (90.0%)	-	Not evaluated	Not evaluated
Okauchi	2022	Present study	98/185 (53.0%)	42/54 (77.8%)	6/6 (100%)	Evaluated	Evaluated

PFS: Progression-free survival; PEM: pemetrexed; EGFR: epidermal growth factor inhibitor; ALK: anaplastic lymphoma kinase.

difference was found in PFS between TTF-1-positive (median PFS: 7.0 months) and TTF-1-negative patients (median PFS: 5.0 months) treated with PEM-containing chemotherapy. In a review by Han *et al.*, the median PFS of patients treated with PEM-containing chemotherapy after EGFR-TKI failure was 5.09 months (28). Kaneda *et al.* reported that in first-line cisplatin plus PEM treatment of 78 *EGFR*-positive patients, the median PFS in the group carrying the L858R mutation and the group with Ex 19 del was 9.4 and 5.5 months, respectively (29). Considering these research results, PFS of patients treated with PEM-containing chemotherapy is considered to reflect real clinical practice. In addition, median PFS of driver gene-negative and driver gene-positive patients treated with PEM-containing chemotherapy was 6.0 and 6.0 months, respectively, and there was no significant difference between them. PEM has often been administered as first-line therapy in driver gene-negative patients, but it is also prescribed as second-line or later therapy in driver gene-positive patients. Even after driver-gene-specific TKI therapy, the efficacy of PEM-containing chemotherapy in patients with driver gene-positive non-sq NSCLC might be as good as that given as first-line to patients with driver gene-negative non-sq NSCLC.

TTF-1 has been associated with PFS of driver gene-negative patients treated with PEM-containing chemotherapy, but not in driver gene-positive patients. The reason for this difference is not clear. In our study, there was

no statistically significant difference in PFS among Groups A, C, and D. There was a significant difference in PFS between these three groups and the driver gene-negative-TTF-1-negative group (Group B). Considering these results together, it is inferred that only Group B shows poor PFS following PEM-containing chemotherapy. In relation to poor PFS in driver gene-negative TTF-1 negative non-sq NSCLC patients, there are some interesting reports (30, 31). Tanaka *et al.* reported that serglycin, a chondroitin sulfate proteoglycan, played a pivotal role in tumor-stromal interaction and reprogramming into an aggressive and immunosuppressive tumor microenvironment in TTF-1-negative lung adenocarcinoma (30). In a report by Matsubara *et al.*, immunohistological expression of TTF-1 correlated with tumor spread through air spaces in the lung cancer lesion, and a poor prognosis in advanced stages (31). However, the mechanism is still unknown.

This study had some limitations. First, although there was no intentional selection bias, it must be pointed out that these were the results of the analysis of the data of patients who were evaluated for TTF-1, and not the results of all patients during the study period. Although patients from three institutions were collected the number is small and the study retrospective. Due to the relationship between the time when this study was conducted and when the driver gene tests became available, it is possible that we were not able to identify driver gene-positive patients other than those

carrying the *EGFR* mutation or the *ALK* rearrangement. In TTF-1 immunohistochemical staining, only “uniform pattern of 50% or more” was regarded as “positive” in this study. This might have influenced the results. It is hypothesized that overall survival might differ between driver gene-positive and -negative patients due to differences in TTF-1, but this study did not analyze overall survival. Based on these limitations, it is expected that further studies will be conducted to confirm and expand our results.

Conclusion

In driver gene-positive non-sq NSLC patients, the presence or absence of TTF-1 was found to have little effect on the response to PEM-containing chemotherapy. In driver gene-positive non-sq NSLC patients, even second-line or later treatment after specific-TKI treatment, PEM-containing chemotherapy could be expected to have the same level of efficacy as first-line PEM-containing chemotherapy in driver gene-negative-TTF-1-positive patients. Regarding PEM-containing chemotherapy in driver-gene positive non-sq NSCLC patients, a similar effect could be expected regardless of the expression of TTF-1.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

SO and HS contributed to the planning, and OS, MK, ST and HS collected data. SO and KM conducted the design and acquisition of data and drafting the manuscript. HS and NH supervised the manuscript. All Authors read and approved the final manuscript.

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