TTF-1 expression is associated with survival in patients with non-squamous non-small cell lung cancer treated with immune checkpoint inhibitor therapy

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Abstract. Thyroid transcription factor-1 (TTF-1) expression has been associated with the prognosis of patients with non-small cell lung cancer treated with immune checkpoint inhibitor (ICI) therapy; however, it has also been suggested that there is no such link. The present study analyzed the association of TTF-1 expression, evaluated using a cocktail antibody (TTF-1/napsin A; clone, SPT24/TMU-Ad02), with survival after the initiation of ICI therapy in patients with EGFR/ALK wild-type non-squamous non-small cell lung cancer receiving first-line treatment with ICI monotherapy or chemoimmunotherapy. A total of 49 patients were enrolled to the present study. Multivariate analysis using the Cox proportional hazard model showed that TTF-1 expression was associated with progression-free survival (PFS) after the initiation of treatment with ICI monotherapy or chemoimmunotherapy (hazard ratio: 0.18, 95% confidence interval: 0.06-0.54). Subset analysis showed that the TTF-1-positive group exhibited significantly longer PFS than the negative group in both the ICI monotherapy (median PFS, 17.6 months vs. 2.9 months, P<0.001, log-rank test) and chemoimmunotherapy (median PFS, 10.4 months vs. 5.2 months, P=0.021, log-rank test) groups. In conclusion, the current study observed an association between TTF-1 expression evaluated using a cocktail antibody and the effectiveness of treatment with ICI monotherapy or chemoimmunotherapy.

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Introduction

The standard of care for advanced non-small cell lung cancer (NSCLC) is systemic therapy. Although cytotoxic agents conferred an improved survival for NSCLC patients with a good performance status (PS) (1), the effectiveness was limited. In this context, molecular targeted therapies and immune checkpoint inhibitors (ICIs) have been developed to improve the prognosis of patients with NSCLC. The effectiveness of ICIs for advanced NSCLC depends on tumor programmed death-ligand 1 (PD-L1) expression. It has been shown that the survival benefit of ICI monotherapy for pre-treated non-squamous NSCLC (2) and chemoimmunotherapy for untreated NSCLC (3) was greater in those with higher PD-L1 expression levels. Thus, tumor PD-L1 expression is considered an indicator of the efficacy of ICI therapy for NSCLC (2).

Alternatively, thyroid transcription factor-1 (TTF-1) expression may be another biomarker for the prognosis of NSCLC. TTF-1 is a transcription factor essential for the development and differentiation of the lung and thyroid. In animal models, its inactivation results in severe malformations (4). Gene amplification of TTF-1 has been demonstrated to promote tumorigenesis in terminal respiratory unit (TRU)-type lung adenocarcinomas (5). Conversely, the loss of TTF-1 transcriptional activity due to inactivating mutations, such as frameshift or nonsense mutations, or promoter methylation has been implicated in the pathogenesis of invasive mucinous adenocarcinomas (6) and non-TRU-type lung adenocarcinomas (7). Moreover, studies employing genetically engineered mouse models have demonstrated the inactivation of TTF-1 promotes the development of mucinous adenocarcinomas and induces a phenotypic shift toward gastric lineage differentiation (8,9).

Given these dual roles of TTF-1 in tumorigenesis, its protein expression has been investigated as a prognostic marker in NSCLC. It is reported that TTF-1 expression is associated with survival after surgery (10), targeted therapy (11), cytotoxic agents (12), and ICI therapy (13-17).

However, multiple antibodies for TTF-1, including 8G7G3/1, SP141, and SPT24, are available, and the optimal antibody for the evaluation of TTF-1 expression is undetermined. Furthermore, opposite findings have been reported concerning the association between TTF-1 expression and survival after the initiation of the ICI therapy (12,18,19). Thus far, the relationship between TTF-1 expression and the therapeutic efficacy of ICIs in NSCLC remains unclear, with existing studies yielding inconsistent or inconclusive results.

Immunohistochemistry for TTF-1 and napsin A using a cocktail antibody (ADC Cocktail antibody, code: KT-17004, prediluted, Pathology Institute, Toyama, Japan) is employed in clinical practice in Japan. Herein, we analyzed the association between TTF-1 expression assessed using a cocktail antibody and survival after ICI therapy.

Patients and methods

Patient selection. We retrospectively analyzed the data of patients with NSCLC. Inclusion criteria were specified as follows: i) Patients who were diagnosed as having non-squamous NSCLC between January 2019 and December 2023 at Toyama University Hospital (Toyama, Japan); ii) patients with inoperable diseases, including advanced, locally advanced, and recurrent NSCLC; iii) patients who received first-line treatment with ICI monotherapy or chemoimmunotherapy (hereafter, ICI therapy); and iv) patients for whom the data regarding TTF-1 expression were evaluated using a cocktail antibody (TTF-1/napsin A). Exclusion criteria were specified as follows: i) Patients with NSCLC showing EGFR mutations and ALK rearrangements; ii) patients with adenosquamous cell carcinoma, sarcomatoid carcinoma, or neuroendocrine carcinoma; and iii) patients for whom important data were unavailable, including PS or PD-L1 expression.

This study was conducted in accordance with The Declaration of Helsinki and the Guideline of Ministry of Health, Labor and Welfare and was approved by the Ethics Committee, University of Toyama (approval no. R2020067). Because this study is retrospective and noninvasive, written informed consent was not required.

Clinical information. Clinical information was collected from medical charts at the initiation of the treatment with ICI therapy, including age, PS, smoking history, disease stage, tumor PD-L1 expression, TTF-1 expression, driver mutation, and treatment history. PD-L1 expression testing was performed by a commercial laboratory (BML INC., Tokyo, Japan) and evaluated using the 22C3 antibody. The expression of TTF-1 was evaluated using a cocktail antibody (code: KT-17004, clone; SPT24/TMU-Ad02, prediluted, Pathology Institute, Toyama, Japan). We performed deparaffinization, antigen retrieval treatment, and endogenous peroxidase blocking using a VENTANA BenchMark ULTRA system (F. Hoffmann-La Roche, Ltd. Basel, Switzerland) according to the manufacturer's instructions.

Statistical analysis. The endpoints of the present study were progression-free survival (PFS) and overall survival (OS) from the initiation of ICI therapy. PFS was calculated from the initiation of ICI therapy to the date of RECIST progressive disease, clinical progression, or death, whichever occurred first, and censored on the day when none of these events was noted. OS was calculated from the initiation of ICI therapy to the date of death and censored on the day of the last visit without death. Kaplan-Meier curve of PFS and OS was drawn, and the median (95% confidence interval, CI) was estimated. PFS and OS were compared using the log-rank test. Multivariate analysis was performed using the Cox progression hazard model to analyze the association between TTF-1 expression and survival, adjusting for potential prognostic factors such as PS, histology, PD-L1 expression, driver mutation, and chemotherapy. Fisher's exact test or Wilcoxon's rank sum test were used to compare patient characteristics. All statistical analyses were performed using JMP version 17.0.0 (SAS, Cary, NC, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Between January 2019 and December 2023, 218 patients with advanced or recurrent NSCLC received first-line treatment with ICI therapy. After excluding 79 patients with EGFR gene mutations or ALK fusion gene positivity, 65 patients with squamous cell carcinoma/adenosquamous carcinoma/sarcomatoid carcinoma/neuroendocrine carcinoma, 20 patients with unknown TTF-1/napsin A status, 4 patients with unknown PD-L1 status, and 1 patient with unknown PS, 49 patients were included in the analysis.

The patient characteristics are summarized in Table I. Among the 49 patients, 14 were negative for TTF-1, and 35 were positive. A higher proportion of cases in the TTF-1-negative group exhibited PD-L1 TPS < 50% than in the positive group. Among the patients with driver gene mutations, there was 1 case of KRAS G12A, 4 cases of KRAS G12C, 1 case of KRAS G12D, 3 cases of KRAS G12V, and 1 case of MET exon 14 skipping mutation. The representative images of positive and negative TTF-1 staining are shown in Fig. S1.

Survival time. Tables II and III show the results of a multivariate analysis adjusted for PS, histology, PD-L1 expression, presence of genetic abnormalities, and the use of chemotherapy. The relationship was examined between TTF-1 expression and both PFS and OS. TTF-1 positivity was significantly associated with a decreased risk of disease progression, independent of these factors; however, no significant association was observed with a decreased risk of death.

Fig. 1 presents the Kaplan-Meier curves for PFS and OS in the TTF-1-positive and -negative groups. The TTF-1-positive group demonstrated significantly longer PFS (median PFS, 15.4 months vs. 4.1 months, $P<0.001$, log-rank test) than the negative group, but not significantly longer OS (median OS, 38.8 months vs. 16.0 months). When patients were stratified by chemotherapy use, the TTF-1-positive group exhibited significantly longer PFS than the negative group in both the ICI monotherapy group (median PFS, 17.6 months vs. 2.9 months, $P<0.001$, log-rank test) and chemoimmunotherapy group (median PFS, 10.4 months vs. 5.2 months, $P=0.021$, log-rank test) (Fig. 2).

Table I. Characteristics of patients with negative and positive TTF-1 expression.

Characteristic	TTF-1		P-value
	Negative	Positive	
Median age, years (range)	72 (60-85)	73 (46-89)	0.894
Sex, n (%)			
Male	11 (78.6%)	26 (74.3%)	>0.999
Female	3 (21.4%)	9 (25.7%)	
PS, n (%)			
0-1	11 (78.6%)	29 (82.9%)	0.702
≥2	3 (21.4%)	6 (17.1%)	
Smoking history, n (%)			
Yes	12 (85.7%)	32 (91.4%)	0.616
No	2 (14.3%)	3 (8.6%)	
Histology, n (%)			
Adenocarcinoma	9 (64.3%)	33 (94.3%)	0.015
Other	5 (35.7%)	2 (5.7%)	
Driver mutation, n (%)			
Positive	3 (21.4%)	7 (20.0%)	>0.999
Negative/unknown	11 (78.6%)	28 (80.0%)	
PD-L1 TPS, n (%)			
<50%	12 (85.7%)	16 (45.7%)	0.013
≥50%	2 (14.3%)	19 (54.3%)	
Stage, n (%)			
3B	0 (0.0%)	1 (2.9%)	0.802
4A	4 (28.6%)	9 (25.7%)	
4B	5 (35.7%)	16 (45.7%)	
Recurrence	5 (35.7%)	9 (25.7%)	
ILD, n (%)			
Yes	2 (14.3%)	2 (5.7%)	0.568
No	12 (85.7%)	33 (94.3%)	
Liver metastases, n (%)			
Yes	1 (7.1%)	2 (5.7%)	>0.999
No	13 (92.9%)	33 (94.3%)	
Brain metastases, n (%)			
Yes	2 (14.3%)	9 (25.7%)	0.475
No	12 (85.7%)	26 (74.3%)	
NLR, n (%)			
<5	6 (42.9%)	24 (68.6%)	0.116
≥5	8 (57.1%)	11 (31.4%)	
LDH, n (%)			
<200 U/l	5 (35.7%)	21 (60.0%)	0.205
≥200 U/l	9 (64.3%)	14 (40.0%)	
CRP, n (%)			
<1.0 mg/dl	7 (50.0%)	23 (65.7%)	0.346
≥1.0 mg/dl	7 (50.0%)	12 (34.3%)	
Treatment, n (%)			
Chemotherapy + ICI	10 (71.4%)	17 (48.6%)	0.207
ICI	4 (28.6%)	18 (51.4%)	

CRP, C-reactive protein; ICI, immune checkpoint inhibitor; ILD, (pre-existed) interstitial lung disease; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PS, performance status; TTF-1, thyroid transcription factor-1.

Table II. Cox proportional hazard model for the risk of progression.

Characteristic	HR	95% CI	P-value
PS			
0-1	0.83	0.27-2.50	0.735
≥2	1.00		
Histology			
Adenocarcinoma	1.27	0.43-3.76	0.666
Other	1.00		
PD-L1 TPS			
≥50%	1.28	0.47-3.47	0.633
<50%	1.00		
Driver mutation			
Positive	0.82	0.32-2.14	0.692
Negative/unknown	1.00		
TTF-1			
Positive	0.18	0.06-0.54	0.002
Negative	1.00		
Treatment			
Chemotherapy + ICI	1.34	0.53-3.43	0.537
ICI	1.00		

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PS, performance status; TTF-1, thyroid transcription factor-1.

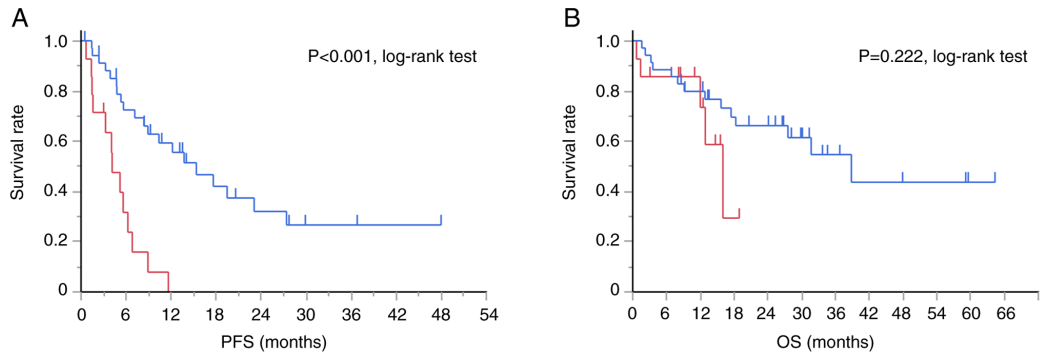

Figure 1. Kaplan-Meier curve for PFS and OS after initiating the treatment with immune checkpoint inhibitor therapy. (A) PFS and (B) OS. Blue line: Patients with TTF-1-positive tumors; red line: Patients with TTF-1-negative tumors. OS, overall survival; PFS, progression-free survival; TTF-1, thyroid transcription factor-1.

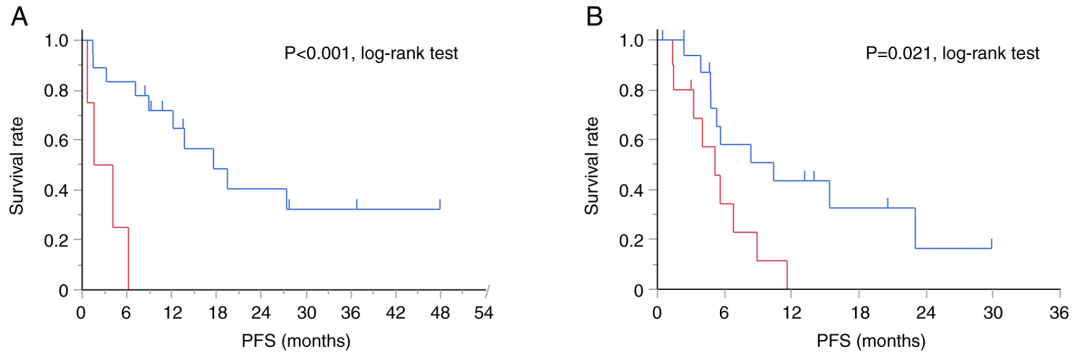

Figure 2. Kaplan-Meier curve for PFS after initiating the treatment with immune checkpoint inhibitor therapy. (A) Patients treated with immune checkpoint inhibitor monotherapy. (B) Patients treated with chemoimmunotherapy. Blue line: Patients with TTF-1-positive tumors; red line: Patients with TTF-1-negative tumors. PFS, progression-free survival; TTF-1, thyroid transcription factor-1.

Table III. Cox proportional hazard model for the risk of death.

Characteristic	HR	95% CI	P-value
PS			
0-1	0.61	0.16-2.41	0.485
≥2	1.00		
Histology			
Adenocarcinoma	0.29	0.08-1.11	0.070
Other	1.00		
PD-L1 TPS			
≥50%	1.15	0.36-3.65	0.818
<50%	1.00		
Driver mutation			
Positive	1.10	0.30-3.98	0.884
Negative/unknown	1.00		
TTF-1			
Positive	0.67	0.15-2.97	0.601
Negative	1.00		
Treatment			
Chemotherapy + ICI	0.81	0.29-2.29	0.694
ICI	1.00		

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PS, performance status; TTF-1, thyroid transcription factor-1.

Discussion

TTF-1 is associated with the survival of NSCLC patients as a prognostic factor. Recently, the relationship between TTF-1 expression and survival after the initiation of ICI therapy has garnered increasing interest, particularly in optimizing treatment strategies for the poor prognostic population characterized by negative TTF-1 expression (18). However, there are inconsistent reports concerning the association between TTF-1 expression and survival. TTF-1 has previously been analyzed using anti-TTF-1 antibody clone 8G7G3/1, SPT24, and SP141 (12,13,15,17-19). The anti-TTF-1 antibody clone SPT24 is more sensitive but less specific than 8G7G3/1 (20). The present study suggests that TTF-1 expression evaluated using a cocktail antibody using SPT24/TMU-Ad02 antibody is associated with PFS after ICI therapy.

TTF-1 is expressed on type II pulmonary epithelial cells and club cells, contributing to lung development and the homeostasis of surfactant protein. TTF-1 induces the expression of myosin-binding protein H, which results in decreased cancer invasion and metastasis (5). Furthermore, several studies have proposed that TTF-1 may also exert tumor-suppressive functions by maintaining alveolar epithelial lineage identity and preventing dedifferentiation. The loss of TTF-1 activity has been implicated in the development of invasive mucinous adenocarcinoma and other non-TRU-type adenocarcinomas (6,7). Thus, the favorable prognosis in patients with TTF-1-positive tumors observed in our study could be partially attributable to its tumor-suppressive function.

Conversely, in TTF-1-negative lung adenocarcinoma, the inactivating mutation of kelch-like ECH-associated protein 1 (KEAP1) is enriched (21), which results in the overexpression of nuclear factor-like 2 (Nrf2), a master regulator of the antioxidant response. Nrf2 is associated with poor prognosis in several cancers, including lung cancer (21). Furthermore, the proportion of PD-L1 positive tumors may be lower in TTF-1-negative NSCLC (14,15), which was observed in the present study. Tumor PD-L1 expression is induced either by oncogene signaling or interferon γ secreted by T lymphocytes (22). Thus, it is hypothesized that T-lymphocyte infiltration is deterred or the function is suppressed in TTF-1-negative non-squamous NSCLC.

There is insufficient information on the association between napsin A expression and clinical outcomes after ICI therapy. Napsin A is an aspartic proteinase expressed on alveolar type 2 cells, contributing to surfactant protein synthase. Immunohistochemistry of napsin A is considered comparable to that of TTF-1 for diagnosing primary lung adenocarcinoma, and dual staining is likely the most beneficial (23,24). Although it is difficult to explain the biological or immunological significance of napsin A expression in relation to ICI therapy for NSCLC, the selection of TTF-1/napsin A-negative non-squamous NSCLC may result in the identification of more poorly differentiated tumors.

The present study has several limitations. First, the sample size was small, which may not sufficiently represent NSCLC patients. Second, given the retrospective nature of the study, the imbalance in patient backgrounds may have affected the

analysis, although multivariate analysis was performed to adjust the potential prognostic factors.

In summary, we observed an association between TTF-1 expression, as evaluated using a cocktail antibody, and the effectiveness of ICI therapy. Further accumulation of data regarding TTF-1 evaluation methodologies and their association with the prognosis of NSCLC patients is necessary.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NM and MI designed the study and wrote the original draft of the manuscript. NM, MI, DF, MH, NT, ZS, KTo, SO, SI, TM and RH contributed to the acquisition of data. KTa and KH contributed to the immunohistochemistry. NM and MI confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with The Declaration of Helsinki and the Guideline of Ministry of Health, Labor and Welfare and was approved by the Ethics Committee, University of Toyama (approval no. R2020067). Because this study is retrospective and noninvasive, written informed consent was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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