

Treatment Response and Survival in Thyroid Transcription Factor-1 Negative Non-squamous Non-small Cell Lung Cancer

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Abstract

Background/Aim: In patients with thyroid transcription factor-1 (TTF-1)-negative non-squamous non-small cell lung cancer (NS-NSCLC), the efficacy of pemetrexed and immunotherapy has been reported to be limited, and the optimal treatment strategy remains unclear. Recent studies have suggested that bevacizumab may improve outcomes; however, robust evidence is still lacking. This study aimed to clarify the clinical characteristics of responders to first-line treatment in patients with TTF-1-negative NS-NSCLC and identify predictive factors for treatment response, proposing an optimal treatment strategy.

Patients and Methods: A retrospective analysis was conducted on patients with TTF-1-negative NS-NSCLC. Patients were classified into responder and non-responder groups based on first-line treatment efficacy, and predictive factors associated with treatment response were analyzed.

Results: Among the 29 patients included, seven (24.1%) were classified as responders. Platinum-based combination therapy was significantly more common in the responder group ($p=0.023$). The neutrophil-to-lymphocyte ratio was significantly lower in the responder group ($p=0.001$). Multivariate analysis demonstrated that the addition of bevacizumab was an independent predictor of treatment response (odds ratio=33.406; 95% confidence interval=1.288-860.210; $p=0.035$). Overall survival was significantly longer in the responder group compared to the non-responder group ($p=0.008$).

Conclusion: In the treatment of TTF-1-negative NS-NSCLC, platinum-based combination therapy, particularly with the addition of bevacizumab, improved response rates and led to prolonged survival.

Keywords: TTF-1, TTF-1-negative NS-NSCLC, bevacizumab, predictive factors, first-line therapy.



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Received May 12, 2025 | Revised July 22, 2025 | Accepted July 28, 2025



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Introduction

Thyroid transcription factor-1 (TTF-1) is an important biomarker for diagnosing and predicting the prognosis of lung adenocarcinoma. TTF-1-negative non-squamous non-small cell lung cancer (NS-NSCLC) has been reported to exhibit biological characteristics similar to squamous cell carcinoma, including distinct gene expression profiles and lower response rates to pemetrexed (PEM) and immune checkpoint inhibitors (ICIs) (1-8). Previous studies have shown that patients with TTF-1-negative NS-NSCLC tend to have poorer treatment outcomes compared to TTF-1-positive cases, with limited benefit from PEM-based chemotherapy and ICIs (2, 9-13). TTF-1 negativity in non-squamous NSCLC is thought to reflect underlying genetic and molecular heterogeneity, which may contribute to differences in tumor behavior and treatment response (14).

Despite these findings, the optimal treatment strategy for TTF-1-negative NS-NSCLC remains unclear. Although recent studies have suggested that the addition of bevacizumab to chemotherapy may improve treatment efficacy in certain subgroups of patients with NS-NSCLC (3, 15), evidence in TTF-1-negative cases is scarce. Moreover, few studies have examined the clinical characteristics and predictive factors associated with treatment response in this population.

Therefore, clarifying effective treatment options for TTF-1-negative NS-NSCLC and identifying predictive factors that may guide first-line treatment selection is essential. This study aimed to investigate the clinical characteristics and predictive factors for treatment response in TTF-1-negative NS-NSCLC, with the goal of optimizing first-line treatment strategies.

Patients and Methods

Study design and data collection. This retrospective study included cases of advanced NSCLC (stage IIIB, IV, or postoperative recurrence) with negative TTF-1 immunostaining. Patients who newly initiated anticancer therapy between December 2016 and December 2024

were analyzed. We collected baseline clinical data at the time of anticancer drug administration, including age, sex, smoking history, performance status (PS), body mass index (BMI), histological subtype of lung cancer, tumor proportion score (TPS), neutrophil-to-lymphocyte ratio (NLR), tumor markers, and treatment details. This study was approved by the Ethics Committee of Kanazawa Medical University Hospital (approval number: C167).

Evaluation of tumor TTF-1 expression. TTF-1 expression was evaluated as part of the routine diagnostic assessment using immunohistochemistry at the time of initial diagnosis. The results of TTF-1 immunostaining were determined based on nuclear staining of tumor cells and were classified as either positive or negative by experienced pathologists.

Tumor response was assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (16). Patients who achieved complete response (CR) or partial response (PR) were classified into the responder group, whereas those with stable disease (SD) or progressive disease (PD) were classified into the non-responder group. Clinical characteristics were compared between these two groups.

Large cell neuroendocrine carcinoma (LCNEC) was excluded from this study, as it was reclassified as small cell lung cancer (SCLC) following the revision of the World Health Organization classification in 2015 (17, 18). Additionally, cases of NSCLC harboring epidermal growth factor receptor (EGFR) mutations were excluded, as the standard first-line treatment for EGFR-mutated NSCLC is molecular targeted therapy (19, 20).

Statistical analysis. All statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). A two-sided p -value of <0.05 was considered statistically significant. Categorical variables were analyzed using the chi-square test, except when the expected frequency was less than 5, in which case Fisher's exact test was applied. Continuous variables were compared between the two groups using an unpaired t -test. Multivariate analysis was conducted using logistic regression.

Table I. Comparison of patient characteristics between responder and non-responder groups.

	Responder group	Non-responder group	p-Value
n (%)	7 (24.1%)	22 (75.9%)	
Age (years), mean (range)	62.9 (29-74)	70.3 (37-83)	0.290
Sex (male/female)	5/2	22/0	0.052
Smoking history (never/prior, current)	5/2	22/0	0.052
ECOG PS (0-1/2-4)	0/7	8/14	0.075
Tumor type (adenocarcinoma/non-adenocarcinoma)	4/3	16/6	0.642
PDL1 expression (22C3) (%) (0/≥1/ untested)	2/5/0	7/10/5	0.316
Clinical stages (IV, postoperative recurrence/ III)	4/3	17/5	0.357
Distant metastasis (yes/no)			
Brain metastasis	0/7	1/21	1.000
Liver metastasis	0/7	3/19	0.557
Platinum agent (initial treatment) (yes/no)	0/7	9/13	0.066
Combination therapy (initial treatment) (yes/no)	2/5	5/17	1.000
ICI monotherapy (initial treatment)			
(yes/no)	0/7	9/13	0.066
PTX (initial treatment)			
(yes/no)	5/2	7/15	0.092
PEM (initial treatment) (yes/no)	1/6	5/17	1.000
BEV (initial treatment) (yes/no)	3/4	2/20	0.075
PEM (entire treatment course) (yes/no)	3/4	5/17	0.282
BMI, no. (range)	23.1 (17.6-27.4)	22.2 (18.5-28.9)	0.529
NLR	2.28 (1.31-4.52)	5.52 (2.10-14.7)	0.001 [‡]

[‡]Based on unpaired *t*-test. ECOG, Eastern Cooperative Oncology Group; TPS, tumor proportion score; combination therapy, combination therapy of immune checkpoint inhibitors and chemotherapy; PTX, paclitaxel; PEM, pemetrexed; BEV, bevacizumab; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio.

For survival analysis, Kaplan-Meier curves were used to estimate survival time, defined as the period from the initiation of lung cancer treatment to death or censoring. The survival analysis was performed in mid-February 2025. Differences in survival between treatment response groups were analyzed using the log-rank test.

Results

Patient background. A total of 29 patients were included. Among them, seven (24.1%) responded to first-line treatment (responder group), whereas 22 (75.9%) did not (non-responder group). Patient characteristics are summarized in Table I. The clinical characteristics and treatment details of the responder group are shown in Table II.

The responder group had a significantly higher proportion of patients receiving platinum-based combination therapy as first-line treatment ($p=0.023$).

Additionally, the NLR was significantly lower in the responder group ($p=0.001$).

Regarding histological subtypes, the responder group included four cases of adenocarcinoma and three cases of NSCLC-not otherwise specified (NOS). The non-responder group comprised 16 cases of adenocarcinoma, five cases of NOS, and one case of pleomorphic carcinoma. No statistically significant difference in histological subtypes was observed between the two groups. Other clinical variables, including age, sex, smoking history, PS, disease stage, or tumor size, showed no significant differences between the groups.

Analysis of predictive factors for treatment response. Univariate and multivariate analyses were performed to identify predictive factors for treatment response in patients with TTF-1-negative NS-NSCLC (Table III).

No statistically significant predictive factors emerged from the univariate analysis. However, multivariate

Table II. Clinical characteristics and treatment details of the responder group.

Case (age/sex)	PS	Pathology	NLR	TPS	Initial treatment regimen	Second-line treatment	Third-line and subsequent treatments
1 (71/M)	0	NOS	2.45	0	CBDCA+nab-PTX+ Pembrolizumab	DTX+RAM	Atezolizumab→ CBDCA+GEM
2 (29/F)	0	Adeno	1.49	0	CDDP+PEM+BEV	DTX+RAM	Atezolizumab→ Gem→ CBDCA+PTX+BEV → VNR→ nab-PTX→ TS-1
3 (73/M)	0	NOS	2.10	50	CBDCA+nab-PTX	None	
4 (64/M)	0	Adeno	1.31	1	Atezolizumab+BEV+ CBDCA+PTX	DTX+RAM	Pembrolizumab→ nab-PTX
5 (72/M)	1	NOS	2.20	5	CBDCA+nab-PTX	Pembrolizumab	DTX+RAM
6 (74/F)	0	Adeno	1.92	45	CBDCA+nab-PTX	None	
7 (57/M)	0	Adeno	4.52	5	CBDCA+PEM+BEV	CBDCA+PTX	Nivolumab→ DTX→ nab-PTX

M, Male; F, female; CBDCA, carboplatin; PTX, paclitaxel; PEM, pemetrexed; TPS, tumor proportion score; DTX, docetaxel; RAM, ramucirumab; GEM, gemcitabine; VNR, vinorelbine; TS-1, tegafur/gimeracil/oteracil; BEV, bevacizumab; PS, performance status.

Table III. Univariate and multivariate analysis of risk factors for non-response to first-line treatment in patients with TTF-1-negative NS-NSCLC.

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Clinical stages (IV, postoperative recurrence vs. III)	0.392 (0.065-2.369)	0.308		
PTX (yes or no)	5.357 (0.826-34.731)	0.078	0.122 (0.007-2.078)	0.146
PEM (yes or no)	1.765 (0.170-18.32)	0.634		
Chemotherapy combination (yes/no)	1.360 (0.200-9.269)	0.754	15.208 (0.433-534.088)	0.134
BEV (yes or no)	7.500 (0.931-60.427)	0.058	33.406 (1.288-866.210)	0.035
TPS (0% vs. ≥1%)	0.571 (0.085-3.833)	0.564		
NLR (<4 vs. ≥4)	8.667 (0.885-84.836)	0.064	8.185 (0.456-146.821)	0.154

OR, Odds ratio; CI, confidence interval; TPS, tumor proportion score; PTX, paclitaxel; PEM, pemetrexed; BEV, bevacizumab; NLR, neutrophil-to-lymphocyte ratio; TTF-1, thyroid transcription factor-1; NS-NSCLC, non-squamous non-small cell lung cancer.

analysis revealed that the addition of bevacizumab independently predicted treatment response [odds ratio (OR)=33.406; 95% confidence interval (CI)=1.288-866.210; $p=0.035$].

Survival analysis. The survival curves for the responder and non-responder groups are shown in Figure 1. The responder group demonstrated a statistically significant survival advantage (log-rank test, $p=0.008$).

Discussion

This study is one of the first to focus exclusively on patients with TTF-1-negative NS-NSCLC, aiming to identify

predictive factors for treatment response and characterize this patient population following first-line treatment. In the present analysis, the use of bevacizumab was significantly associated with a higher likelihood of achieving a treatment response (OR=33.406; 95% CI=1.288-866.210; $p=0.035$). Although the CI was wide – likely due to the limited number of events – the result suggests a potential therapeutic benefit of bevacizumab in this subset of patients. Previous studies have reported the efficacy of platinum plus taxane plus bevacizumab combination therapy in TTF-1-negative NSCLC (3) and atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) regimen (15).

Iso *et al.* suggested that bevacizumab may enhance the efficacy of atezolizumab by transforming the immuno-

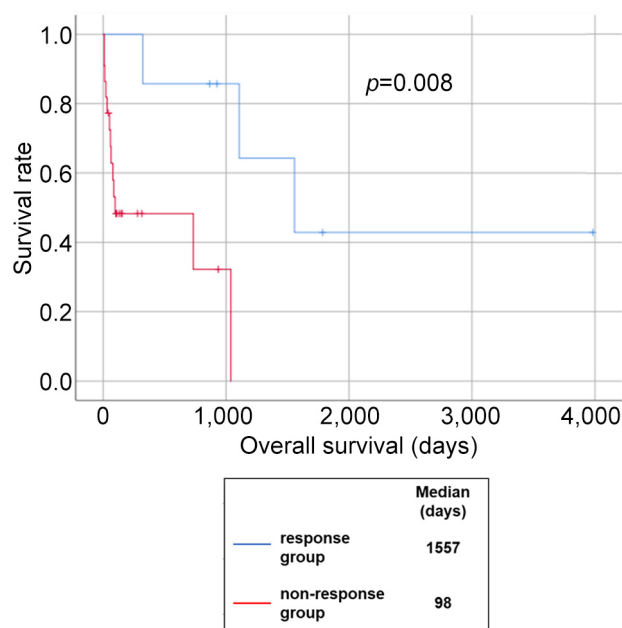


Figure 1. Overall survival of patients in the responder and non-responder groups. The median survival time was 1,557 days in the responder group and 98 days in the non-responder group. A significant difference was observed between the two groups ($p=0.008$, log-rank test).

suppressive tumor microenvironment in patients with TTF-1-negative NSCLC into an immunostimulatory state through vascular endothelial growth factor (VEGF) inhibition. However, in this study, only one patient in the responder group received ABCP therapy, whereas the remaining two received a combination of bevacizumab and chemotherapy. Conversely, some reports suggest that adding bevacizumab does not provide clinical benefit for TTF-1-negative lung cancer (21). The inconsistencies among studies may stem from differences in patient characteristics, programmed death-ligand 1 (PD-L1) expression levels, or treatment regimens. These findings highlight the potential efficacy of bevacizumab-containing regimens in patients with TTF-1-negative NS-NSCLC; however, given the conflicting evidence, further accumulation of cases and robust analysis are warranted.

When comparing platinum-based combination therapy with ICI monotherapy, we found that patients who received platinum-based combination therapy as first-line

treatment were significantly more common in the responder group. In contrast, no patients in the responder group received ICI monotherapy. This finding aligns with previous reports suggesting that ICI monotherapy has limited efficacy in TTF-1-negative lung adenocarcinoma (12). Therefore, for individuals with TTF-1-negative NSCLC, platinum-based combination therapy or combination therapy with ICIs appears to be a more appropriate option than ICI monotherapy. However, for patients with poor PS, treatment decisions should be carefully individualized.

Regarding the NLR, although it was significantly lower in the responder group, multivariate analysis did not identify it as an independent predictive factor for treatment response. Although NLR has been recognized as a predictive factor for ICI treatment response (22-26), this study included cases that did not receive ICI therapy as first-line treatment, potentially introducing bias due to the heterogeneity of treatment backgrounds. Furthermore, differences in baseline systemic inflammation levels and disease burden may have influenced the results. Future large-scale cohort studies with uniform ICI treatment backgrounds are warranted to better understand the prognostic value of NLR in TTF-1-negative NSCLC.

Regarding the use of PEM and taxane-based agents (PTX), the responder and non-responder groups showed no significant difference in PEM regimen use. This finding contradicts previous reports suggesting that PEM demonstrates limited efficacy in TTF-1-negative NSCLC (3, 27-31). Several factors, including the small sample size, variations in treatment lines, and challenges in assessing the isolated effect of PEM monotherapy, may explain this discrepancy. Further research is needed to clarify the role of PEM in this setting.

Similarly, PTX use did not differ significantly between the two groups, and multivariate analysis did not identify it as a predictive factor for treatment response. However, some studies have reported that taxane-based agents may be effective regardless of TTF-1 staining results (2). Given the potential benefit of taxane-based chemotherapy in NSCLC, taxane-based regimens may serve as a reasonable

option for first-line treatment, whereas PEM may be incorporated into subsequent lines of therapy.

In this study, a substantial difference was observed in median overall survival between responders and non-responders (557 vs. 98 days). TTF-1-negative non-squamous NSCLC is recognized as a biologically aggressive subtype that frequently exhibits limited responsiveness to systemic therapies. In the present cohort, patients who failed to respond to initial treatment experienced rapid disease progression and had limited opportunities for subsequent therapy, resulting in markedly shorter survival. Although the number of cases was relatively small, these findings underscore the prognostic significance of achieving an early treatment response in this population. The possibility remains that the magnitude of the observed survival difference was influenced by the limited sample size; thus, additional studies with larger cohorts are needed for validation.

Study limitations. Firstly, the retrospective, single-institutional design may have reduced the generalizability of the findings. Secondly, although the sample size permitted the detection of some statistically significant associations, the small number of cases may have affected the stability of the multivariate models. The low number of responders raised the potential for overfitting in the multivariate analysis. Efforts were made to minimize this by selecting clinically relevant covariates; nonetheless, confirmation using larger datasets remains necessary. Thirdly, the retrospective observational nature of the study limited the ability to control for selection bias and confounding variables. Fourthly, although immortal time bias was a theoretical concern when comparing responders and non-responders, this bias was unlikely to have applied in the present analysis because all patients survived at least until the first response assessment. Finally, treatment decisions were made at the discretion of attending physicians, resulting in variability in therapeutic strategies. Given these limitations, further validation through prospective studies and large-scale cohort research is necessary.

Conclusion

Platinum-based combination therapy and bevacizumab-containing regimens enhanced treatment response and prolonged survival in patients with TTF-1-negative NS-NSCLC receiving first-line treatment. In contrast, ICI monotherapy demonstrated limited efficacy, indicating that platinum-based combination therapy or ICI-based combination therapy may serve as more suitable options. These findings highlight the importance of selecting appropriate first-line treatments for TTF-1-negative NS-NSCLC. Further prospective studies are warranted to refine treatment strategies and improve patient outcomes.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

All Authors had full access to the study data and took responsibility for the integrity of the data and the accuracy of the data analysis. All the Authors have read and approved the submission of this manuscript. Conceptualization: Y. T.; Resources: Y. T., R. A., S. N., T. T., Y. I., I. S., K. Y., M. N., and M.I.; Investigation: R. A., S. N., T. T., Y. I., I. S., K. Y., M. N., and M.I.; Methodology: Y. T. and M. I.; Writing – original draft: Y. T., with support from M.I.

Acknowledgements

None.

Funding

This study received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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