Original Article

Prognostic impact of negative TTF-1 biomarker in metastatic lung adenocarcinoma treated with chemo-immunotherapy: a retrospective cohort study

Luis Posado-Domínguez[1,2]^, Alejandro Olivares-Hernández[1,2], Daniel Morchón-Araujo[1,2], Luis Figuero-Perez[1,2], Lorena Bellido-Hernández[1,2], Laura Corvo-Felix[1,2], Jonnathan Roldan-Ruiz[1,2], Iñigo San Miguel[2,3], Emilio Fonseca-Sanchez[1,2,4], Edel Del Barco-Morillo[1,2,4]

[1]Medical Oncology Department, University Hospital of Salamanca, Salamanca, Spain; [2]Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; [3]Radiation Oncology Department, University Hospital of Salamanca, Salamanca, Spain; [4]Faculty of Medicine, University of Salamanca, Salamanca, Spain

Contributions: (I) Conception and design: L Posado-Dominguez, A Olivares-Hernández, D Morchón-Araujo; (II) Administrative support: E Del Barco-Morillo, E Fonseca-Sanchez; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: L Posado-Dominguez, A Olivares-Hernández, L Bellido-Hernández, E Del Barco-Morillo; (V) Data analysis and interpretation: L Posado-Dominguez, A Olivares-Hernández; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Luis Posado-Domínguez, MD; Alejandro Olivares-Hernández, PhD. Medical Oncology Department, University Hospital of Salamanca, Paseo de San Vicente, 182, 37007, Salamanca, Castilla-León, Spain; Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Castilla-León, Spain. Email: luisposado@usal.es; aolivares@saludcastillayleon.es.

Background: The prognostic significance of TTF-1 expression in advanced lung adenocarcinoma may be an important factor in optimizing treatment strategies. This study aimed to evaluate the impact of TTF-1 negativity on overall survival (OS) and progression-free survival (PFS) in stage IV lung adenocarcinoma patients with low PD-L1 expression treated with platinum-pemetrexed-pembrolizumab.

Methods: We conducted a retrospective analysis of 155 patients with stage IV lung adenocarcinoma and PD-L1 expression <50%. We stratified patients according to TTF-1 expression. The primary survival analysis focused on 64 patients who received first-line platinum-pemetrexed chemotherapy in combination with pembrolizumab. We evaluated OS and PFS using Kaplan-Meier curves and multivariate Cox regression.

Results: Among patients treated with platinum-pemetrexed-pembrolizumab, TTF-1-negative patients showed significantly shorter OS and numerically shorter PFS compared to TTF-1-positive patients. Median OS was 13 months for TTF-1-negative patients and 21 months for TTF-1-positive patients (P=0.01). Median PFS was 10 *vs.* 13 months, respectively (P=0.11). In the overall cohort, TTF-1 negativity was independently associated with a 2.3-fold increased risk of mortality (hazard ratio =2.288, 95% confidence interval: 1.073–4.879, P=0.03).

Conclusions: TTF-1 negativity is an independent adverse prognostic factor in patients with stage IV lung adenocarcinoma and low PD-L1 expression. The observed differences in survival suggest that platinum-pemetrexed-pembrolizumab may be less effective for TTF-1-negative patients, and that alternative strategies should be explored in this high-risk subgroup.

Keywords: TTF-1; PD-L1; pemetrexed; KRAS; lung adenocarcinoma

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^ ORCID: 0009-0005-4606-2316.

Introduction

In 2022, 2,480,675 cases of lung cancer were diagnosed, accounting for 12.4% of all neoplasms and ranking first in global incidence. Approximately 75% of the diagnoses occurred in men (1,572,045). Lung cancer was also the leading cause of cancer-related mortality, with a total of 1,817,469 deaths, representing 18.7% of all cancer deaths (1).

Histologically, approximately 85% of new lung cancer diagnoses are non-small-cell lung cancer (NSCLC). Among these, during the 1960s and 1970s, squamous cell carcinoma was the most common subtype. However, its incidence has progressively decreased over the past decades in favor of adenocarcinoma, which now represents approximately 40–50% of NSCLC diagnoses (2).

This change in histological distribution has increased interest in the molecular characterization and use of biomarkers in lung adenocarcinoma. One of the most relevant biomarkers for determining the best treatment is PD-L1 expression, which is routinely measured in all subtypes of NSCLC to guide the use of immunotherapy (ICI) alone or in combination with chemotherapy (chemo) (3). Despite being used as a cutoff to select different treatment options in the pivotal trials for ICI approval in NSCLC, it is an imperfect marker, and its negativity does not rule out a possible good response to ICI. Therefore, caution is needed when classifying PD-L1-negative patient subgroups as non-responders, necessitating the ongoing search for better alternatives and more robust biomarkers (4,5).

On the other hand, the search for actionable genomic alterations—such as *EGFR* mutations, and *ALK* or *ROS1* rearrangements or gene fusions—is routinely performed in patients with lung adenocarcinoma, where these alterations are more prevalent. Additionally, mutations in genes such as *BRAF*, *MET*, and *KRAS* have also emerged as therapeutic targets, with drugs approved in the second line of treatment showing promising results (6).

While therapeutic advances have improved outcomes in selected patients, the prognostic relevance of certain biomarkers—such as TTF-1—remains insufficiently addressed.

TTF-1, also known as NKX2-1, is a transcription factor encoded by the *NKX2-1* gene, located on chromosome 14q13. It plays an essential role in the normal development of the lungs and thyroid gland, and is physiologically expressed in type 2 pneumocytes and cells of the bronchiolar epithelium (7,8). In immunohistochemical studies, TTF-1 is positive in most cases of lung adenocarcinoma, with reported expression rates of 60–80% (9). Due to its frequent expression, TTF-1 has traditionally been used as a diagnostic marker to distinguish lung adenocarcinomas from other metastatic tumors in the thorax. (10). In addition to its diagnostic value, TTF-1 expression has been associated with a more favorable prognosis in patients with lung adenocarcinoma, as its presence often indicates greater tumor differentiation and better treatment response. It has been suggested that differentiating lung adenocarcinoma patients based on TTF-1 expression may be clinically relevant. A lower response to pemetrexed has been observed in TTF-1-negative (TTF-1$^-$) patients (11). Despite its potential prognostic value, TTF-1 expression has not been routinely incorporated into randomized clinical trials or treatment guidelines. This gap may be due to the lack of standardized assessment protocols, variability in reporting across institutions, and the absence of prospective evidence supporting its role in therapeutic decision-making. This lack of inclusion in clinical trials and standardization in clinical practice underscores the need for further investigation into the prognostic role of TTF-1 and its potential to guide treatment selection. The main objective of this study is to evaluate the prognostic significance of TTF-1 in patients with metastatic lung adenocarcinoma.

Highlight box

Key findings

- TTF-1 negativity was independently associated with significantly worse overall survival and progression-free survival in stage IV lung adenocarcinoma patients with low PD-L1 expression treated with platinum-pemetrexed-pembrolizumab.

What is known and what is new?

- TTF-1 has been traditionally used as a diagnostic marker in lung adenocarcinoma and is often associated with better tumor differentiation and prognosis.
- This study adds new evidence supporting the role of TTF-1 as a prognostic biomarker, specifically in the subset of PD-L1 low expressors treated with chemo-immunotherapy, where TTF-1 negativity identifies a high-risk population with poor outcomes.

What is the implication, and what should change now?

- Current treatment decisions in lung adenocarcinoma rely heavily on PD-L1 expression and actionable mutations, often overlooking other prognostic markers.
- TTF-1 status should be routinely reported and considered in clinical decision-making. For TTF-1-negative patients, alternative chemotherapy strategies beyond pemetrexed-based combinations should be explored to improve outcomes.

We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-65/rc).

Methods

A retrospective cohort analysis was conducted to evaluate the prognostic relevance of the biomarker TTF-1 in patients with metastatic lung adenocarcinoma and low PD-L1 expression (<50%). The study included 155 adult patients (>18 years) diagnosed with stage IV lung adenocarcinoma at the Medical Oncology Department of the University Hospital of Salamanca between January 1, 2020, and July 1, 2024. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Ethics Committee of the Salamanca University Hospital Complex (No. 2022-10-1155), and written informed consent was obtained from all participants.

We excluded patients with *EGFR* mutations or *ALK* or *ROS1* rearrangements who were eligible for an approved first-line targeted therapy according to European Medicines Agency guidelines at the time of diagnosis. Similarly, patients with oligometastatic disease who underwent surgical resection or stereotactic body radiation therapy (SBRT) as part of their first-line treatment were excluded.

Out of the 155 eligible patients, TTF-1 expression data were available for 136. We used immunohistochemical analysis to evaluate the presence or absence of the TTF-1 marker. Among them, 118 patients had complete clinical and molecular data and were included in the baseline descriptive analysis (*Table 1*). For survival analysis, two complementary subgroups were defined:

- A group of 84 patients with PD-L1 expression <50% and available TTF-1 status, in whom overall survival (OS) was analyzed based on TTF-1 expression, regardless of the treatment received.
- A more homogeneous subgroup of 64 patients with PD-L1 <50% who received first-line platinum-pemetrexed chemotherapy in combination with pembrolizumab, in whom both OS and progression-free survival (PFS) were analyzed.

Clinical and molecular variables collected included: age (median, and dichotomized at 75 years), Eastern Cooperative Oncology Group performance status (ECOG PS, 0–1, 2, or 3), sex, smoking status (smoker *vs.* non-smoker), and cumulative pack-year index (IPA). Metastatic burden was recorded as the number of metastatic sites (1–2 *vs.* ≥3) and by specific location (bone, adrenal, brain), as determined by computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) imaging. Molecular data included mutational status of *KRAS*, *TP53* and *EGFR*. TTF-1 expression was assessed by immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded (FFPE) tissue sections using the monoclonal antibody clone SPT24 (Cell Marque, Rocklin, CA, USA; Merck/Sigma-Aldrich, St. Louis, MO, USA) was used. Nuclear staining was considered positive. PD-L1 expression was assessed by IHC using the 22C3 pharmDx assay (Agilent/Dako, Glostrup, Denmark), and quantified as Tumor Proportion Score (TPS). Patients with TPS <50% were classified as low expressors.

Information on first-line treatment was collected, including type of chemotherapy or chemo-immunotherapy administered. The best response to treatment was assessed using RECIST criteria (progression, stable disease, partial response, or complete response). Data on second-line therapy and treatment received at the last cycle were also recorded.

Statistical analyses

Statistical analyses were performed using RStudio (version 2023.09). Continuous variables were summarized as medians and interquartile ranges (IQR), while categorical variables were reported as absolute and relative frequencies. Group comparisons were made using the Mann-Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Survival outcomes (OS and PFS) were assessed using Kaplan-Meier curves and compared using the log-rank test. A multivariate Cox proportional hazards regression model was used to identify independent prognostic factors, reporting hazard ratios (HR) with 95% confidence intervals (CIs). A two-sided P value <0.05 was considered statistically significant.

Missing data were handled with variable-by-variable exclusion, and the total number of cases analyzed was reported in each table. No imputation methods were used due to the limited extent of missing data.

Survival curves were generated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Multivariate analysis was performed using Cox proportional hazards models to identify independent prognostic factors for OS and PFS. The following covariates were included: TTF-1 expression, number of

Table 1 Clinical, molecular and treatment characteristics of stage IV lung adenocarcinoma patients based on TTF-1 expression (n=118[†])

Variable	TTF-1^{+}	TTF-1^{-}	Total	P value
Age (years)	69 (67–70)	68 (63–72)	69 (67–70)	
≥75	93 (78.8)	15 (83.3)	108 (79.4)	0.66
<75	25 (21.2)	3 (16.7)	28 (20.6)	
ECOG PS				0.07
0–1	93 (78.8)	13 (72.2)	106 (77.9)	
2	17 (14.4)	1 (5.6)	18 (13.2)	
3	8 (6.8)	4 (22.2)	12 (8.8)	
Sex				0.32
Male	93 (78.8)	16 (88.9)	109 (80.1)	
Female	25 (21.2)	2 (11.1)	27 (19.9)	
Tobacco				0.11
Smoker	99 (86.8)	17 (100)	116 (88.5)	
Non smoker	15 (13.2)	0 (0)	15 (11.5)	
Status				0.56
Alive	40 (34.5)	5 (27.8)	45 (33.6)	
Deceased	76 (65.5)	13 (72.2)	89 (66.4)	
IPA (pack-years)	40 (31.5–41.6)	47 (32.7–65.2)		0.20
Number metastases				0.34
1–2	91 (77.1)	12 (66.7)	103 (75.7)	
>3	27 (22.9)	6 (33.3)	33 (24.3)	
Bone metastases				0.02
Yes	50 (42.4)	13 (72.2)	63 (46.3)	
No	68 (57.6)	5 (27.8)	73 (53.7)	
Adrenal metastases				0.053
Yes	22 (18.8)	7 (38.9)	29 (21.5)	
No	95 (81.2)	11 (61.1)	106 (78.5)	
CNS metastases				0.052
Yes	21 (17.8)	0 (0)	21 (15.4)	
No	97 (82.2)	18 (100)	115 (84.6)	
KRAS mutated	33 (34)	7 (38.9)	40 (34.8)	
KRAS wild type	64 (66)	11 (61.1)	75 (65.2)	0.70
KRAS mutation				0.71
KRAS G12C	20 (62.5)	7 (100)	27 (69.2)	
KRAS G12V	5 (15.6)	0 (0)	5 (12.8)	
KRAS Q61H	2 (6.3)	0 (0)	2 (5.1)	
KRAS G13C	1 (3.1)	0 (0)	1 (2.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable (N=118†)	TTF-1⁺	TTF-1⁻	Total	P value
KRAS G13D	2 (6.3)	0 (0)	2 (5.1)	
KRAS G12D	1 (3.1)	0 (0)	1 (2.6)	
KRAS G12A	1 (3.1)	0 (0)	1 (2.6)	
TP53 mutated	12 (10.2)	3 (16.7)	15 (11)	
TP53 wild type	106 (89.8)	15 (83.3)	121 (89)	0.41
EGFR mutated	5 (4.3)	1 (5.6)	6 (4.5)	
EGFR wild type	110 (95.7)	17 (94.4)	127 (95.5)	0.82
EGFR INS20	3 (60)	1 (100)	4 (66.7)	
EGFR amplification	2 (40)	0 (0)	2 (33.3)	0.44
1st line treatment				0.07
Pemetrexed + ICI	60 (50.8)	11 (61.1)	71 (52.2)	
Pembro	43 (36.4)	2 (11.1)	45 (33.1)	
Carboplatin	7 (5.9)	4 (22.2)	11 (8.1)	
Chemo-amivantamab	1 (0.8)	0 (0)	1 (0.7)	
BSC	7 (5.9)	1 (5.6)	8 (5.9)	
Best response				0.68
PD	35 (31.5)	7 (41.2)	42 (32.8)	
SD	20 (18)	2 (11.8)	22 (17.2)	
PR	51 (45.9)	8 (47.1)	59 (46.1)	
CR	5 (4.5)	0 (0)	5 (3.9)	
2nd line treatment				0.14
Yes	43 (39.8)	3 (20)	46 (37.4)	
No	65 (60.2)	12 (80)	77 (62.6)	
Lines				0.24
First	39 (53.4)	10 (83.3)	49 (55.7)	
Second	17 (23.3)	1 (8.3)	18 (20.5)	
Third	9 (12.3)	0 (0)	9 (10.2)	
Fourth	2 (2.7)	1 (8.3)	3 (3.4)	
Fifth+	6 (8.2)	0 (0)	6 (6.8)	
PD-L1				0.01
<50%	68 (58.1)	16 (88.9)	84 (62.2)	
≥50%	49 (41.9)	2 (11.1)	51 (37.8)	

Data are presented as median (interquartile range, IQR) for continuous variables and as number (percentage) for categorical variables, unless otherwise specified. †, data shown correspond to 118 patients with available clinical and molecular information. Although TTF-1 status was known in 136 patients, 18 were excluded from this table due to missing data in one or more variables. Percentages are calculated based on the number of available cases for each variable. BSC, best supportive care; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IPA, index of pack-years; PD, progressive disease; PR, partial response; SD, stable disease.

metastases, *TP53* status, *KRAS* status, ECOG PS, and age (≥75 *vs.* <75 years). HR and 95% CI were reported. Statistical significance was set at P<0.05.

Sample analysis

Descriptive analysis of clinical, molecular and treatment characteristics of stage IV lung adenocarcinoma patients according to TTF-1 expression

The median age was similar in both groups, 69 years in TTF-1-positive (TTF-1$^+$) patients (95% CI: 66.6–70.1%) and 68 years in TTF-1$^-$ patients (95% CI: 63.1–71.7); P=0.66. Regarding PS, measured by the ECOG scale, most TTF-1$^+$ patients had ECOG 0–1 (78.8%), while in the TTF-1$^-$ group there was a higher proportion of patients with ECOG 3 (22.2% *vs.* 6.8%). Although the difference was not statistically significant (P=0.07), it suggests that TTF-1$^-$ patients may have a more deteriorated PS. Most patients were male in both groups (78.8% in TTF-1$^+$ and 88.9% in TTF-1$^-$, P=0.32). Among TTF-1$^+$ patients, 86.8% were smokers, whereas the percentage was 100% in TTF-1$^-$ patients (P=0.11). The IPA was 47 in TTF-1$^-$ patients compared to 40 in TTF-1$^+$ patients.

There was a higher proportion of bone metastases in the TTF-1$^-$ group (72.2% *vs.* 42.4%, P=0.02). The number of patients with adrenal metastases was also higher in this group (38.9% *vs.* 18.1%, P=0.053). Regarding central nervous system (CNS) involvement, none of the TTF-1$^-$ patients had brain metastases compared to 17.8% of TTF-1$^+$ patients (P=0.052). With respect to PD-L1 status, a higher proportion of high expressors was observed in the TTF-1$^+$ group compared to the TTF-1$^-$ group (41.9% *vs.* 11.1%, P=0.01). Finally, regarding *KRAS* mutations, G12C accounted for 62.5% of *KRAS* mutations in the TTF-1$^+$ group and 100% of *KRAS* mutations in the TTF-1$^-$ group. Further clinical characteristics for this group can be found in *Table 1*. A distribution of the *KRAS* mutations observed in the entire sample can be found in Figure S1.

Descriptive analysis of clinical, molecular, and treatment characteristics in stage IV lung adenocarcinoma patients with PD-L1 <50%, stratified by TTF-1 expression

A total of 84 patients with stage IV lung adenocarcinoma and PD-L1 expression <50% were included in the analysis. Patients were stratified according to TTF-1 expression to assess differences in clinical, molecular, and treatment-related variables (*Table 2*).

The median age was similar between groups: 68 years (IQR, 60–72 years) in TTF-1$^+$ patients and 70 years (IQR, 59–75 years) in TTF-1$^-$ patients. No statistically significant difference was found in the distribution of patients ≥75 years (14.7% in TTF-1$^+$ *vs.* 18.8% in TTF-1$^-$, P=0.70).

Most patients had an ECOG PS of 0–1, without significant differences between groups (79.4% in TTF-1$^+$ *vs.* 68.8% in TTF-1$^-$, P=0.11). Similarly, male sex was predominant in both groups (80.9% in TTF-1$^+$ *vs.* 93.8% in TTF-1$^-$, P=0.21). A higher proportion of patients in the TTF-1$^+$ group were active or former smokers (85.1%) compared to the TTF-1$^-$ group (100%), although this difference was not statistically significant (P=0.11).

Regarding vital status, 44 of 68 (64.7%) TTF-1$^+$ patients had died at the time of analysis, compared to 13 of 16 (81.3%) among TTF-1$^-$ patients (P=0.26).

In terms of disease burden, a trend was observed toward a higher number of metastatic sites in the TTF-1$^-$ group, with 37.5% of patients presenting with ≥3 metastatic sites compared to 19.1% in the TTF-1$^+$ group (P=0.11). Bone metastases were more frequent in the TTF-1$^-$ group (68.8% *vs.* 50.0%), though not statistically significant (P=0.18). However, adrenal metastases were significantly more common in the TTF-1$^-$ group (43.8% *vs.* 13.4%, P=0.006). Interestingly, brain metastases were only observed in TTF-1$^+$ patients (16.2%), while no TTF-1$^-$ patients presented CNS involvement (P=0.08).

Regarding molecular alterations, the prevalence of *KRAS* mutations was similar between groups (33.3% in TTF-1$^+$ *vs.* 37.5% in TTF-1$^-$, P=0.75). Among patients with KRAS mutations, the G12C subtype accounted for 100% of cases in the TTF-1$^-$ group, compared to 62.5% in the TTF-1$^+$ group, showing a trend toward significance (P=0.057). No significant differences were found in *TP53* status (P=0.82).

As for first-line treatment, most patients received a combination of platinum-based chemotherapy with pemetrexed and pembrolizumab (79.4% in TTF-1$^+$ *vs.* 68.8% in TTF-1$^-$, P=0.31). The best response to treatment (according to RECIST criteria) was not significantly different between groups (P=0.31). However, a significantly lower proportion of TTF-1$^-$ patients received second-line treatment (14.3% *vs.* 49.2%, P=0.02), suggesting earlier deterioration or limited therapeutic benefit in this group.

OS analysis of low PD-L1 expressors based on TTF-1 (*Table 3*)

The median follow-up period was 20 months (m). The expression of TTF-1 was associated with statistically

Table 2 Clinical, molecular and treatment characteristics of stage IV lung adenocarcinoma with PD-L1 <50% patients based on TTF-1 expression (n=84[†])

Variable	TTF-1$^+$	TTF-1$^-$	Total	P value
Age (years)				0.70
≥75	58 (14.7%)	13 (18.8%)	71 (84.5%)	
<75	10 (85.3%)	3 (81.2%)	13 (15.5%)	
ECOG PS				0.11
0–1	54 (79.4%)	11 (68.8%)	65 (77.4%)	
2–3	14 (20.6%)	5 (31.2%)	19 (22.6%)	
Sex				0.21
Male	55 (80.9%)	15 (93.8%)	70 (83.3%)	
Female	13 (19.1%)	1 (6.2%)	14 (16.7%)	
Tobacco				0.11
Smoker	57 (85.1%)	15 (100%)	72 (87.8%)	
Non smoker	10 (14.9%)	0 (0%)	10 (12.2%)	
Status				0.26
Alive	22 (33.3%)	3 (18.8%)	25 (30.5%)	
Deceased	44 (66.7%)	13 (81.2%)	57 (69.5%)	
Number metastases				0.11
1–2	55 (80.9%)	10 (62.5%)	65 (77.4%)	
>3	13 (19.1%)	6 (37.5%)	19 (22.6%)	
Bone metastases				0.18
Yes	34 (50%)	11 (68.8%)	45 (53.6%)	
No	34 (50%)	5 (31.2%)	39 (46.4%)	
Adrenal metastases				0.006
Yes	9 (13.4%)	7 (43.8%)	16 (19.3%)	
No	58 (86.6%)	9 (56.2%)	67 (80.7%)	
CNS metastases				0.08
Yes	11 (16.2%)	0 (0%)	11 (13.1%)	
No	57 (83.8%)	16 (100%)	73 (86.9%)	
KRAS mutated	22 (33.3%)	6 (37.5%)	28 (34.1%)	
KRAS wild type	44 (66.7%)	10 (62.5%)	54 (65.9%)	0.75
KRAS G12C	13 (59.1%)	6 (100%)	19 (67.9%)	
KRAS other	9 (40.9%)	0 (0%)	9 (32.1%)	0.057
TP53 mutated	10 (14.7%)	2 (12.5%)	12 (14.3%)	
TP53 wild type	58 (85.3%)	14 (87.5%)	72 (85.7%)	0.82

Table 2 (*continued*)

Table 2 (*continued*)

Variable	TTF-1$^+$	TTF-1$^-$	Total	P value
1st line treatment				0.31
Pemetrexed + ICI	54 (79.4%)	11 (68.8%)	65 (77.4%)	
Pembro	2 (2.9%)	0 (0%)	2 (2.4%)	
Carboplatin	5 (7.4%)	4 (25%)	9 (10.7%)	
Chemo-amivantamab	1 (1.5%)	0 (0%)	1 (1.2%)	
BSC	6 (8.8%)	1 (6.2%)	7 (8.3%)	
Best response				0.31
PD	15 (24.2%)	7 (46.7%)	22 (28.6%)	
SD	11 (17.7%)	2 (13.3%)	13 (16.9%)	
PR	32 (51.6%)	6 (40%)	38 (49.4%)	
CR	4 (6.5%)	0 (0%)	4 (5.2%)	
2nd line treatment				0.02
Yes	31 (49.2%)	2 (14.3%)	33 (42.9%)	
No	32 (50.8%)	12 (85.7%)	44 (57.1%)	

†, data shown correspond to 84 patients with available TTF-1 status and PD-L1 expression <50%. Percentages are calculated within each TTF-1 group (column-wise). In some variables, the total may not sum to 84 due to missing data. BSC, best supportive care; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3 OS and PFS in stage IV lung adenocarcinoma patients by TTF-1 expression

Variable	N	OS		PFS	
		Median survival (95% CI), months	P value	Median survival (95% CI), months	P value
TTF-1			0.004		0.03
Positive	68	20 (15.5–24.5)		9 (6.7–11.3)	
Negative	16	6 (0.6–11.5)		4 (0.1–7.9)	
All	84	16 (7.7–24.2)		8 (6.7–9.3)	
Platinum-peme-pembro			0.01		0.11
TTF-1$^+$	53	21 (17.0–24.9)		13 (8.8–17.2)	
TTF-1$^-$	11	13 (5.5–20.5)		10 (5.1–14.9)	

"Platinum-Peme-Pembro" refers to platinum (cisplatin or carboplatin), pemetrexed, and pembrolizumab combination. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

significant differences in OS and PFS. TTF-1$^+$ patients had a median OS of 20 months (95% CI: 15.5–24.5) compared to 6 months (95% CI: 0.6–11.5) in TTF-1$^-$ patients (P=0.004) (*Figure 1*). Similarly, PFS was better in TTF-1$^+$ patients, with a median of 9 months (95% CI: 6.7–11.3) compared to 4 months (95% CI: 0.1–7.9) in the TTF-1$^-$ group (P=0.03).

A stratified survival analysis was performed based on TTF-1 expression, including patients with low PD-L1 expression (PD-L1 <50%) treated with chemo combined with ICI (platinum-pemetrexed-pembrolizumab) and with chemo alone (carboplatin). In the group treated with

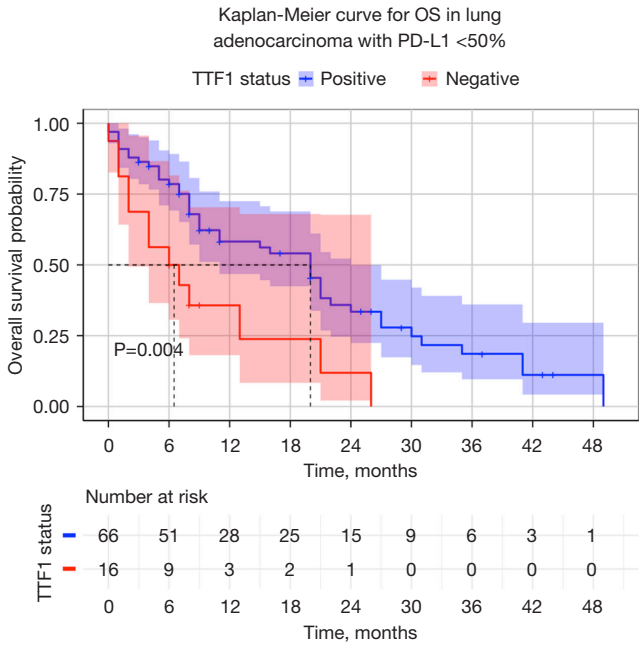

Figure 1 Kaplan-Meier curve for OS in lung adenocarcinoma patients with low PD-L1 expression (<50%), stratified by TTF-1 status. OS, overall survival.

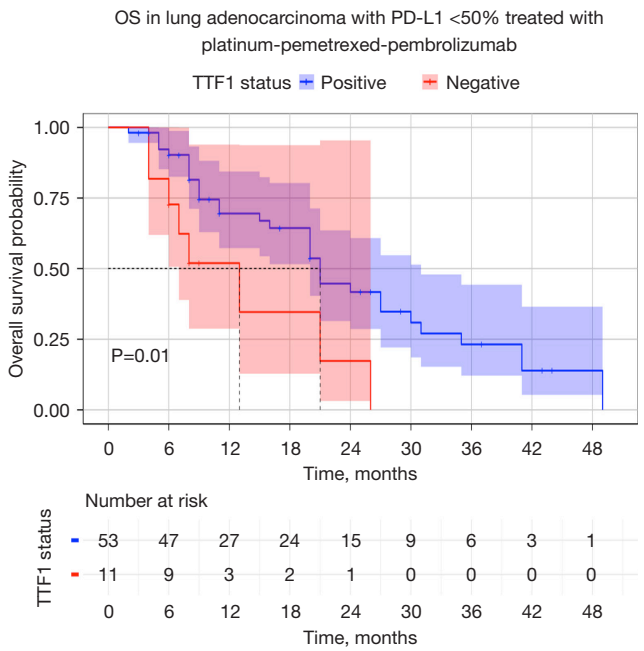

Figure 2 Kaplan-Meier curve for OS in lung adenocarcinoma patients with low PD-L1 expression (<50%) who received 1L treatment with platinum-pemetrexed-pembrolizumab, stratified by TTF-1 status. OS, overall survival.

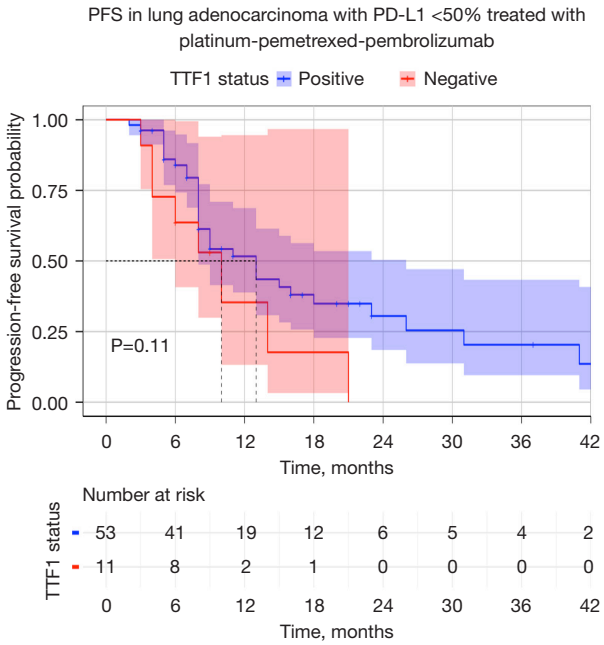

Figure 3 Kaplan-Meier curve for PFS in lung adenocarcinoma patients with low PD-L1 expression (<50%) who received 1L treatment with platinum-pemetrexed-pembrolizumab, stratified by TTF-1 status. PFS, progression-free survival.

platinum-pemetrexed-pembrolizumab, TTF-1$^+$ patients (n=53) had an OS of 21 months (95% CI: 17.0–24.9), which was significantly higher than the 13 months (95% CI: 5.5–20.5) observed in TTF-1$^-$ patients (n=11) (P=0.01) (*Figure 2*). PFS was also better in TTF-1$^+$ patients, with a median of 13 months (95% CI: 8.8–17.2) compared to 10 months (95% CI: 5.1–14.9) in TTF-1$^-$ patients, although this difference did not reach statistical significance (P=0.11) (*Figure 3*).

In the group treated with carboplatin, the results showed a trend towards worse survival in TTF-1$^-$ patients, with an OS of 1 month (95% CI: 0–2.3) compared to 4 months (95% CI: 0–10.4) in TTF-1$^+$ patients (P=0.12). PFS was similarly low in both groups, with a median of 1 month, without significant differences (P=0.24). These findings suggest that carboplatin monotherapy has limited efficacy in these patients.

Multivariate analysis in low PD-L1 expressors

In the multivariate analysis conducted on the cohort of low PD-L1 expressors, we found that TTF-1 negativity, *KRAS* mutation, and PS measured by ECOG scale were

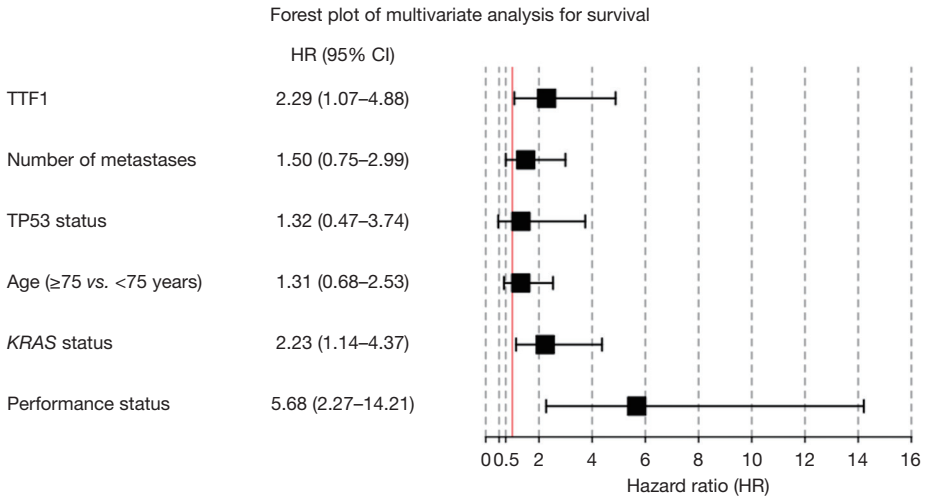

Figure 4 Forest plot of the multivariate survival analysis for patients with stage IV lung adenocarcinoma. CI, confidence interval; HR, hazard ratio.

significantly associated with independent prognostic factors for survival.

The TTF-1 variable showed a significant association with survival, with an HR of 2.29 (95% CI: 1.07–4.88; P=0.03), indicating that negative TTF-1 expression is associated with an increased risk of mortality in this patient population. The mutated *KRAS* status was significantly associated with survival, with an HR of 2.23 (95% CI: 1.14–4.37; P=0.02). This indicates that the presence of a *KRAS* mutation is a negative prognostic factor in this population, significantly increasing the risk of mortality. A worse PS measured by the ECOG scale was negatively associated with survival, with an HR of 5.68 (95% CI: 2.27–14.21; P<0.001). Regarding the number of metastases, although a higher number was associated with an HR of 1.50, it did not reach statistical significance (95% CI: 0.75–2.99; P=0.25). Mutated *TP53* status was associated with a worse prognosis, with an HR of 1.320, but it did not reach statistical significance (95% CI: 0.47–3.74; P=0.6). Although age over 75 years implied a worse prognosis, with an HR of 1.32, it also did not reach statistical significance (95% CI: 0.68–2.53; P=0.41). The data can be found in Table S1 and *Figure 4*.

Discussion

Prognostic significance of TTF-1

In this retrospective study, we evaluated the prognostic significance of the biomarker TTF-1 in patients with metastatic lung adenocarcinoma. Our findings highlight that TTF-1$^-$ is associated with worse OS and PFS, underscoring its potential role as an adverse prognostic marker in this population. It is important to note that, due to the observational and retrospective nature of our study, these findings demonstrate an association between TTF-1 negativity and poor survival outcomes, but do not establish a direct causal relationship. In our sample, TTF-1$^-$ patients had significantly lower median OS (6 *vs.* 20 months, P=0.004). In the multivariate analysis, TTF-1$^-$ was associated with a 2.3-fold increased risk of mortality compared to TTF-1$^+$ patients (HR =2.288, 95% CI: 1.073–4.879, P=0.03), reinforcing its importance as an independent prognostic factor and supporting the notion that loss of TTF-1 expression could indicate a more aggressive tumor phenotype. These findings are consistent with those of Da Cruz *et al.* (12), who also found that TTF-1 negativity was significantly associated with worse survival in a retrospective cohort of 253 stage IV lung adenocarcinoma patients. In their multivariate analysis, TTF-1$^+$ patients had a significantly lower risk of death (HR =0.64, 95% CI: 0.42–0.98, P=0.04) and a median OS of 11.2 *vs.* 4.0 months for TTF-1-negative cases. Their data support the notion that TTF-1 loss identifies a subgroup with a more aggressive tumor phenotype, even when adjusting for age, performance status, and treatment type.

TTF-1 and PD-L1 expression

We observed a low prevalence of TTF-1$^-$ in combination

with high PD-L1 expression (≥50%), with only 3.9% of TTF-1$^-$ patients showing high PD-L1 expression. This low frequency of TTF-1$^-$ patients with high PD-L1 expression limits the interpretability of potential interactions between TTF-1 status and PD-L1 expression in our cohort. Due to the small sample size of this subgroup, no firm conclusions can be drawn regarding the prognostic or predictive implications of TTF-1 negativity in the context of high PD-L1 expression. In comparison with our results, Iso *et al.* found no significant differences in PD-L1 expression based on TTF-1 status (13). On the other hand, Nakahama *et al.* observed a higher prevalence of PD-L1 ≥50% in TTF-1$^+$ patients compared to TTF-1$^-$ patients (65% *vs.* 24%), although in lower proportions than in our sample (14). A possible explanation for this lower PD-L1 expression could be related to the findings of Yatabe *et al.* (9), who suggested a distinct origin for adenocarcinomas based on TTF-1 expression. According to their hypothesis, TTF-1$^+$ adenocarcinomas originate from the terminal respiratory unit (TRU), which consists of small bronchioles and terminal respiratory cells, while TTF-1$^-$ adenocarcinomas may derive from more central lung cells or structures different from the TRU, such as columnar or metaplastic cells (12,15). This difference in cellular origin could explain the more aggressive profile observed in TTF-1$^-$ adenocarcinomas, which is associated with a higher frequency of mutations in genes such as *TP53* (9,16). However, this remains a theoretical model, and our study does not provide molecular or histological validation of this hypothesis. Additionally, *KRAS* mutations—particularly the G12C subtype—were observed at a slightly higher frequency in our cohort compared to other published series. This may be explained by the fact that our study exclusively included patients with metastatic disease at diagnosis, a subgroup typically associated with more aggressive tumor behavior. In such cases, *KRAS* mutations are often more prevalent. Nonetheless, the difference in frequency was modest and remains consistent with the expected range in metastatic lung adenocarcinoma, where *KRAS* mutations are generally found in approximately one-third of patients.

Recent molecular studies have suggested that the prognostic implications of TTF-1 negativity may be linked to underlying genetic alterations in NKX2-1, the gene encoding this transcription factor. In a comprehensive genomic and epigenomic analysis, Snyder *et al.* (2013) demonstrated that NKX2-1 loss-of-function alterations, including homozygous deletions and methylation silencing, are enriched in poorly differentiated lung adenocarcinomas with aggressive features, and are associated with reduced TTF-1 protein expresión (17). Furthermore, Saito *et al.* (2009) found that NKX2-1-deficient tumors display a unique transcriptomic signature, including epithelial-mesenchymal transition (EMT) activation and loss of alveolar differentiation, which may contribute to therapeutic resistance and early metastatic dissemination (15,18). Complementing these findings, He *et al.* (2024) identified NKX2-1 inactivation as a cooperating event with TP53 and KRAS mutations in preclinical models, promoting a dedifferentiated state and decreased immune cell infiltration (19). Taken together, these studies provide biological support for the clinical observations reported in our cohort, where TTF-1$^-$ tumors exhibited more aggressive dissemination patterns, lower response to pemetrexed-based regimens, and significantly worse survival outcomes. Although our study did not perform molecular profiling of NKX2-1, future research should aim to integrate IHC with genomic data to better understand the molecular basis of TTF-1 loss and its prognostic significance in advanced lung adenocarcinoma.

Impact of treatment in TTF-1-negative patients

We observed that patients with low PD-L1 expression who received platinum-based chemo with pemetrexed in combination with pembrolizumab showed notable differences in survival based on TTF-1 expression. TTF-1$^+$ patients had significantly better OS, with a median of 21 months (95% CI: 17.0–24.9), compared to 13 months (95% CI: 5.5–20.5) in TTF-1$^-$ patients (P=0.01). PFS was also better in TTF-1$^+$ patients, with a median of 13 months (95% CI: 8.8–17.2) compared to 10 months (95% CI: 5.1–14.9) in TTF-1$^-$ patients; however, this difference did not reach statistical significance (P=0.11).

These results suggest that the platinum-pemetrexed doublet in combination with ICI may not be the most effective option for improving survival in TTF-1$^-$ patients, who exhibit more aggressive and less differentiated histological characteristics. It is necessary to consider alternative treatments or personalized approaches for this patient population.

Our findings are consistent with previous studies. Frost *et al.* reported an OS of 4.1 months in TTF-1$^-$ patients treated with platinum-pemetrexed compared to 8.0 months in those treated with pemetrexed-free regimens (P=0.001). Additionally, PFS was significantly longer in patients without pemetrexed (3.6 *vs.* 6 months, P=0.001). These data

highlight the limited effectiveness of platinum-pemetrexed in this subpopulation, particularly in the absence of ICI (11). In a similar context, Iso *et al.* (2023) analyzed 14 TTF-1$^-$ patients treated with chemo and ICI, reporting an OS of 32.3 months (95% CI: 3.19–61.41) (13). Within this group, patients who received platinum-pemetrexed-pembrolizumab had an OS of 11.7 months and a PFS of 7.1 months, while those treated with carboplatin-paclitaxel-bevacizumab-atezolizumab (CBDCA-PTX-BEV-ATZ) showed a median OS that was not reached and a PFS of 22.5 months (15). This suggests that the observed benefit may depend on the specific Chemo-ICI regimen used (13). Nishioka *et al.* (2024) also reported encouraging results in TTF-1$^-$ patients treated with different chemo-ICI regimens, with a median OS not reached (95% CI: 21.1–NA) and a PFS of 15.5 months (20). Although they did not find significant differences between TTF-1$^+$ and TTF-1$^-$ patients treated with chemo-ICI, the study highlights the heterogeneity of outcomes depending on the specific regimen. Finally, Uhlenbruch showed that TTF-1$^-$ patients treated with chemo-ICI (N=23) had significantly worse PFS compared to TTF-1$^+$ patients (N=41), with 3 *vs.* 9 months, respectively (P=0.001) (18). The lack of specification of the regimen used limits direct interpretation, but the overall impact of TTF-1 expression appears consistent with other studies showing a poorer prognosis in TTF-1$^-$ patients. Given the limited efficacy of platinum-pemetrexed combinations observed in TTF-1$^-$ patients, and their more aggressive and less differentiated histological profile, it is plausible that this subgroup might benefit from alternative chemotherapy regimens, such as platinum-paclitaxel, which are more commonly used in squamous histology. Although no patients in our cohort were treated with this regimen, this hypothesis merits further investigation.

We observed a higher proportion of bone metastases (72.2% *vs.* 42.4%, P=0.02) and adrenal metastases (38.9% *vs.* 18.8%, P=0.053) in TTF-1$^-$ patients, although significance was not reached for adrenal metastases. Regarding CNS involvement, no TTF-1$^-$ patients presented with brain metastases, compared to 17.8% of TTF-1$^+$ patients. These results are consistent with those reported by Frost *et al.*, who also observed a higher frequency of adrenal and bone metastases in the TTF-1$^-$ Group (11). These differences in the distribution of metastases suggest that TTF-1$^-$ patients exhibit a distinct and potentially more aggressive pattern of dissemination, which could influence the selection of treatment strategies and clinical management.

Our findings support the need for a more refined histomolecular stratification in metastatic lung adenocarcinoma. Recent work by Désage *et al.* has proposed a more clinically applicable classification that integrates histopathological features, oncogenic mutations, and tumor microenvironment characteristics, including immune cell composition and DNA methylation profiles (21). Such approaches might help identify distinct subgroups of patients—such as TTF-1$^-$ tumors harboring *KRAS* or *TP53* mutations—with poorer prognoses and potential resistance to immunotherapy. Incorporating these multidimensional data into clinical decision-making may guide the selection of more effective, personalized treatment strategies beyond current PD-L1-based models.

A comparative summary of results from various studies analyzing the impact of treatment in lung adenocarcinoma patients based on PD-L1 expression can be found in *Table 4*.

This study presents several potential biases inherent to its retrospective design. The data comes from clinical databases of a single institution, which limits the generalizability of the results. Moreover, the quality and availability of clinical data may have influenced the results, as some records could be incomplete or inaccurate. The lack of randomization also implies a higher risk of confounding bias, as the impact of unobserved variables could not be fully controlled.

However, it is important to note that the study was conducted within the Spanish National Health System, which provides universal and free access to oncologic treatments. This ensured equitable access to the best available therapies during the study period, minimizing variability related to treatment availability or socioeconomic status.

Importantly, data on *STK11* and *KEAP1* mutations were not routinely available during the study period, despite their known relevance in predicting response to immunotherapy. Another limitation of this study is the presence of missing data in some clinical and molecular variables. We addressed this by performing a variable-by-variable exclusion approach in the corresponding analyses, including only patients with available information for each variable. While the proportion of missing data was low and unlikely to have substantially impacted the results, we acknowledge that the absence of imputation methods may have reduced the robustness of some subgroup comparisons. Additionally, specific data regarding treatment modifications, such as dose reductions, delays, or early discontinuations, were not consistently recorded in the clinical databases used. As a result, we could not assess how these variations might have influenced survival outcomes. Although all patients received treatment in accordance with standard clinical practice,

Table 4 Review of available studies on OS and PFS in lung adenocarcinoma patients based on TTF-1 expression

Study	Year	Patients	Treatment regimen	OS (months)	OS P value	PFS (months)	PFS P value
Nakahama (14)	2022	TTF-1$^+$ (N=83)	ICI (pembrolizumab, nivolumab or ATZ)	18.2	0.041	5.4	<0.001
		TTF-1$^-$ (N=25)		8.0		1.6	
Iso (13)	2023	TTF-1$^+$ (N=45)	Chemo-ICI[†]	18.9 (14.02–23.78)	0.78	9.6	0.14
		TTF-1$^-$ (N=14)		32.3 (3.19–61.41)		9.9	
		TTF-1$^-$ (N=4)	Platinum-Peme-Pembro	11.7	NA	7.1	NA
		TTF-1$^-$ (N=4)	CBDCA/nab-PTX/ICI	7.4		8.2	
		TTF-1$^-$ (N=6)	CBDCA/PTX/BEV/ATZ	NR		22.5	
		TTF-1$^+$ (N=40)	ICI	17.5	0.15	4.5	0.088
		TTF-1$^-$ (N=18)		15.6		3.8	
Frost (11)	2020	TTF-1$^+$ (N=235)	Pemetrexed based chemo	12.1	0.001[§]	5.4	0.001[§]
		TTF-1$^-$ (N=58)		4.1		3.6	
		TTF-1$^+$ (N=155)	Non-pemetrexed based[‡]	12.3		6.8	
		TTF-1$^-$ (N=81)		8		6	
Moeller (22)	2022	TTF-1$^+$ (N=119)	NA[¶]	8.4	0.27	6.5	0.16
		TTF-1$^-$ (N=35)		5.8		4.6	
Park (23)	2019	TTF-1$^+$ (N=27)	Chemotherapy	19.3	<0.001	4.9	0.004
		TTF-1$^-$ (N=59)		5.8		3.0	
Schilsky (24)	2017	TTF-1$^+$ (N=249)	Pemetrexed based chemo	16.0	ND	5.7	ND
		TTF-1$^-$ (N=69)		8.5		3.1	
		TTF-1$^+$ (N=39)	Non-pemetrexed based	14.2		3.4	
		TTF-1$^-$ (N=11)		9.3		2.4	
Uhlenbruch (18)	2024	TTF-1$^+$ (N=40)	ICI	NA	NA	18	0.004
		TTF-1$^-$ (N=26)				5	
		TTF-1$^+$ (N=41)	Chemo-ICI	NA		9	0.001
		TTF-1$^-$ (N=23)				3	
Nishioka (20)	2024	TTF-1$^+$ (N=120)	Pembrolizumab[#]	29.9	0.74	6.8	0.51
		TTF-1$^-$ (N=46)		21.8		4.9	
		TTF-1$^+$ (N=75)	Chemo-ICI	NR (42.6–NA)	0.62	20.5	0.78
		TTF-1$^-$ (N=25)		NR (21.1–NA)		15.5	

[†], includes patients treated with platinum/pemetrexed/pembrolizumab, CBDCA/nab-paclitaxel/immunotherapy, and CBDCA/paclitaxel/bevacizumab/atezolizumab. CBDCA stands for carboplatin. [‡], in the non-pemetrexed regimen, it includes combinations of platinum with gemcitabine, taxane, vinorelbine, and other regimens. [§], P value compares TTF-1-negative groups only. [¶], includes patients treated with chemotherapy, immunotherapy, chemo-immunotherapy, tyrosine kinase inhibitors, radiotherapy, and supportive care. [#], chemo-immunotherapy includes platinum (cisplatin or carboplatin)/pemetrexed/pembrolizumab, platinum (cisplatin or carboplatin)/nab-paclitaxel/pembrolizumab, carboplatin/paclitaxel/bevacizumab/atezolizumab, and carboplatin/nab-paclitaxel/atezolizumab regimens. ATZ, atezolizumab; BEV, bevacizumab; CBDCA, carboplatin; ICI, immune checkpoint inhibitor; NA, not available; ND, not calculated; NR, not reached; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel.

this lack of granularity represents another limitation of the study. Furthermore, the relatively small size of the TTF-1$^-$ subgroup reflects its lower prevalence in advanced-stage disease and represents a limitation of this study. Moreover, the sample size is relatively small in some subgroups, which could limit the statistical significance of the findings. Finally, although the median follow-up duration was adequate to capture survival outcomes in most patients, we acknowledge that longer follow-up may provide a more complete understanding of late events such as delayed progression, long-term survival, or late treatment-related toxicities—particularly in high-risk subgroups. Future studies with extended follow-up periods will be important to confirm the durability of these findings.

Conclusions

The present study highlights the significant prognostic impact of TTF-1 negativity in patients with stage IV lung adenocarcinoma and low PD-L1 expression treated with platinum-pemetrexed-pembrolizumab. TTF-1$^-$ patients showed significantly worse OS and PFS, suggesting that TTF-1 could serve as an important prognostic marker in this population.

While our findings suggest that the standard platinum-pemetrexed-pembrolizumab regimen may be less effective in TTF-1$^-$ patients, further research is needed to determine whether alternative chemotherapy strategies could offer improved outcomes. Future prospective studies should investigate whether TTF-1 expression could help refine risk stratification and guide treatment decisions in advanced lung adenocarcinoma.

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None.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-65/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Ethics Committee of the Salamanca University Hospital Complex (No. 2022-10-1155), and informed consent was obtained from all participants prior to their inclusion in the study.

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