Lung Cancer 210 (2025) 108853

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

AXL expression to predict resistance to immunotherapy in metastatic non-small cell lung cancer

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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Immunotherapy
AXL
Biomarker
Resistance

ABSTRACT

Background: Non-small cell lung cancer (NSCLC) remains a major therapeutic challenge. While PD-1/PD-L1 immunotherapies have improved outcomes, predictive biomarkers are limited. AXL, a receptor tyrosine kinase associated with poor prognosis, may impact treatment response. This study evaluates AXL expression and clinical outcomes in advanced NSCLC patients treated with immunotherapy or chemotherapy.

Methods: This retrospective study included 89 metastatic NSCLC patients treated at the University Hospital of Reims (2015–2023) with either anti-PD-1 therapy or chemotherapy. Clinical data and outcomes—progression-free survival (PFS) and overall survival (OS)—were analyzed. AXL expression was assessed by immunohistochemistry, and propensity score matching adjusted for prognostic variables.

Results: AXL-positive tumors were associated with shorter PFS (4.3 vs. 5.3 months, $p = 0.044$). Immunotherapy improved PFS (7.6 vs. 4.4 months, $p = 0.006$) and response rate (48 % vs. 22 %) compared to chemotherapy. However, AXL-positive patients derived less benefit from immunotherapy; IO-treated AXL-negative patients had significantly better PFS ($p = 0.003$) and OS ($p = 0.018$). Multivariate analysis identified AXL as an independent factor for poorer PFS (HR 4.15, $p = 0.013$) and OS (HR 5.634, $p = 0.004$). KRAS and STK11 mutations were more frequent in AXL-positive tumors.

Conclusions: AXL expression is associated with reduced immunotherapy efficacy in NSCLC and may serve as a predictive biomarker and therapeutic target.

1. Introduction

Lung cancer continues to be a major global health issue, with its prevalence increasing and resulting in 2.2 million new cases in 2020 [1]. Non-small cell lung cancer (NSCLC) is the most common histological type, accounting for 80 % of cases. In the past decade, the treatment landscape for advanced and metastatic NSCLC has fundamentally changed with the introduction of immunotherapy (IO). These monoclonal antibodies target immune checkpoints such as PD-1/PD-L1, enabling the host immune system to generate a response against tumor cells, potentially leading to durable clinical responses [2]. Table 1..

Positive results have thus led to the registration of IO as the standard treatment for NSCLC based on PD-L1 expression levels. For any PD-L1 expression level, it is thus possible to combine IO with chemotherapy (CT), resulting in a median PFS increase of approximately 3 months and nearly doubling the median OS, in accordance with KEYNOTE 407 [3] and KEYNOTE 189 [4] trials. It is also possible to propose IO alone to a selected patient population with high PD-L1 expression (≥50 % of tumor proportion score (TPS)), based on data from KEYNOTE 024 [5,6], IMPower 110 [7] and EMPOWER-Lung 1 [8] for Pembrolizumab, Atezolizumab and Cemiplimab, respectively.

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https://doi.org/10.1016/j.lungcan.2025.108853
Received 21 July 2025; Received in revised form 26 September 2025; Accepted 21 November 2025
Available online 22 November 2025

Table 1
Clinicopathological characteristics of the original cohort (n = 89).

		No. (%) [range] n = 89
Age, median		64 [42–83]
	< 65 years	46 (51.7 %)
	≥ 65 years	43 (48.3 %)
Body mass index (kg/m^2)		23.4 [13.4–42.3]
Gender (Male / Female)		55 / 34
Smoking history		
	Never / Former	61 (68.5 %)
	Current smokers	28 (31.5 %)
PDL1 expression (TPS)		
	< 50 %	50 (56.2 %)
	≥ 50 %	32 (36 %)
	Unknown	7 (7.9 %)
Histological sub-type		
	Adenocarcinoma	64 (71.9 %)
	Squamous	22 (24.7 %)
	Other	3 (3.4 %)
Stage *		
	IIIA/IIIB	5 (5.6 %)
	IV	84 (94.4 %)
Regimen		
	CT alone	52 (58.4 %)
	IO alone	14 (15.7 %)
	CT-IO combination	23 (25.8 %)
PS-ECOG		
	0–1	78 (87.6 %)
	2	11 (12.4 %)
Metastatic sites		
	Liver metastasis	7 (7.9 %)
	CNS metastasis	22 (24.7 %)

PDL1: Programmed Death-Ligand 1, TPS: tumor proportion score, CT; Chemotherapy, IO: Immunotherapy, PS-ECOG: Eastern Cooperative Oncology Group – Performance Status, CNS: central nervous system. Data are expressed as median [range] or n(%), as appropriate.
* Eighth Edition of the TNM Classification for Lung Cancer.

Despite the significant impact of IO on NSCLC management, identifying which patients will benefit the most remains a clinical challenge [9]. Currently, PD-L1 expression assessed through immunohistochemistry is the most widely used biomarker for predicting response to IO and remains the only marker integrated into clinical practice. However, incomplete predictive power and inter-assay variability, highlight the necessity for alternative predictive biomarkers [10–12].

AXL is a receptor tyrosine kinase belonging to the TYRO3-AXL-MERTK (TAM) kinase family [1]. Dysregulation of AXL expression has been observed in various cancers of diverse histological origins, including melanoma, gastrointestinal cancers, head and neck neoplasms, and breast cancer [2]. AXL expression has also been reported in thoracic malignancies such as mesothelioma [3] and NSCLC. High levels of AXL have been associated with poor prognosis in several solid tumors, including NSCLC [2]. AXL also facilitates epithelial-to-mesenchymal transition (EMT) [13]. Intracellular signalling by AXL positively regulates transcription factors essential for EMT, including TWIST, ZEB1, ZEB2, and SLUG. It promotes N-cadherin expression while decreasing E-cadherin expression to induce EMT, as reported in NSCLC [14]. EMT is broadly reported as a mechanism of resistance to various therapies, including anti-PD1 antibodies [15]. Upon binding to AXL, the ligand GAS6 regulates cell signalling cascades and communication within the tumor microenvironment, involving cancer cells, endothelial cells, and immune cells [16]. Cumulative evidence supports AXL as a promising molecular target to address therapy resistance and immunosuppression [17].

Based on its biological impact, we explored the clinical implications of tumor AXL expression on patient outcomes in advanced NSCLC treated with anti-PD1 therapies, compared with a CT control group.

2. Methods

2.1. Patients' selection

This retrospective single-center study, conducted at the University Hospital of Reims, France, included 89 advanced (unresectable stage IIIA/IIIB not eligible for definitive chemoradiation [non-irradiable]) or metastatic NSCLC patients without actionable genetic alterations (AGAs) who received with first-line IO (either as monotherapy or in combination with CT) between September 2015 and March 2023: chemotherapy (CT) alone, immunotherapy (IO) alone, or IO in combination with CT. Patients were classified into the CT group if they received CT alone and into the IO group if they received IO either as monotherapy or in combination with CT.

The inclusion criteria were as follows: 1) patients aged 18 years or older with metastatic NSCLC treated at the University Hospital of Reims, France, 2) first-line treatment with CT alone, IO alone, or IO + CT, and 3) availability of clinical data. The exclusion criteria included: 1) non-NSCLC histology, 2) NSCLC with AGAs in first-line treatment, 3) no remaining tumor tissue available for AXL assessment, and 4) prior treatment for NSCLC in earlier stages (including radiation and/or systemic therapies).

Baseline clinical characteristics such as age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, histology, TNM stage derived from pre-therapeutic PET/CT scans, and smoking status, along with PD-L1 Tumor Proportion Score (TPS), initiation date of the first treatment course, treatment line, specific immune checkpoint inhibitor (ICI) administered, initial follow-up date, and either the date of death or the most recent contact, were collected from the patient's medical records.

2.2. Survival analysis

For each patient included in the study, detailed clinical and biological data were collected before starting IO and/or CT. Following established clinical guidelines, IO or CT were continued until either disease progression or the occurrence of adverse effects. PFS was measured from the start of treatment until disease progression, as identified by CT scan, or until death or the last follow-up. OS was determined from the initiation of treatment to either death or the last follow-up.

Treatment responses were evaluated using the RECIST (Response Evaluation Criteria in Solid Tumors) criteria, specifically version 1.1 as described by Eisenhauer in 2009 [18]. When CT-based evaluation was impractical according to RECIST guidelines, or when the patient's condition deteriorated rapidly, response was assessed through clinical and laboratory methods. These cases were included in the OS analysis but excluded from the PFS analysis per RECIST criteria. The scans and medical records were reviewed by two experienced clinicians, blinded to the AXL expression values.

2.3. Immunohistochemistry analysis

Sections of 3-μm were obtained from formalin-fixed paraffin-embedded blocks of NSCLC. After antigen retrieval in Target Retrieval Solution, pH 9 (Dako, Glostrup, Denmark) and endogenous peroxidase inhibition in Bloxall Blocking Solution (Vector Laboratories, Burlingame, CA, USA), tissue sections were incubated with the primary anti-AXL rabbit polyclonal antibody (1:250; cat. no. PA5-77875; Invitrogen) for 1 h at room temperature. Samples were subsequently washed with PBS and incubated with the ImmPress HRP Reagent kit peroxidase anti-Rabbit IgG (Vector Laboratories). HRP activity was revealed with the ImmPACT NovaRED peroxidase substrate kit (Vector Laboratories), according to the manufacturer's protocol. Whole slide images were captured using an inverted slide scanner equipped with a Pike IEEE1394b camera and a 20X objective (VS120; Olympus Corporation, Tokyo, Japan). AXL expression was then evaluated by a qualified

pathologist by a tumor proportion score (TPS), blinded to clinical outcomes.

2.4. Molecular analysis

Molecular profiling was obtained from formalin-fixed paraffin-embedded (FFPE) tissue samples. Tumor cellularity was assessed on hematoxylin and eosin–stained slides by a pathologist, and macro-dissection was performed when tumor content was below 20 % to enrich for neoplastic cells. Total nucleic acids (TNA) were extracted from five consecutive 5-µm sections using the Maxwell CSC RNA FFPE kit (Promega), with overnight proteinase K digestion and without DNase treatment. Library preparation was carried out from the RNA fraction using a custom 50-gene RNA sequencing panel based on Agilent's SureSelectXT HS capture technology, after reverse transcription (among targeted genes: EGFR, KRAS, BRAF, MET, HERBB2, STK11, KEAP1, SMARCA4, ALK, ROS1, RET, NRG1, NTRK1/2/3). Targeted RNAseq libraries were sequenced on an Illumina MiSeq platform (100 cycles, paired end). Sequencing data were analyzed using the SomaRNA bioinformatics pipeline implemented on the SeqOne platform, enabling the detection of single nucleotide variants, short insertions/deletions, and fusion transcripts. Standard quality control metrics (including sequencing depth, base quality, alignment rate, and duplicate read rate) were applied.

2.5. Statistical analysis

The data were presented as medians and ranges for quantitative variables and as counts and percentages for qualitative variables. Associations between features were analyzed using the Fisher test. Quantitative data were evaluated using non-parametric tests, such as the Mann–Whitney or Kruskal–Wallis tests, to determine significance across different conditions. Proportions (ORR, DCR) were compared using Fisher's exact test. Survival analysis was performed using the Kaplan–Meier method, with significance assessed through the log-rank test and Cox regression where appropriate.

Propensity score matching was conducted using 1:1 matching without replacement (greedy-matching algorithm), with a caliper width equal to 0.1 of the standard deviation of the logit of the propensity score. The "timeROC" R package (https://cran.r-project.org/web/packages/timeROC/index.html) was used to compare the AUCs of ROC curves for predicting PFS and OS based on varying levels of AXL expression. Oncoprint visualization was performed using tools available at https://docs.cbioportal.org/. In all exploratory analyses, a two-sided p-value 0.05 was considered statistically significant. Data analysis and formatting were conducted using XLSTAT software (version 2023.3.1 (1416), Addinsoft, Paris, France) and R software (v 4.3.2).

2.6. Ethical consideration

This retrospective observational study was approved by the University Hospital of Reims' data protection departments (MR004160420221). Information notices for non-opposition were sent to patients living at the time of data collection, in accordance with French law.

3. Results

3.1. Patient characteristics

We first screened 160 patients with an advanced NSCLC and treated in the first line by chemotherapy (CT) alone or in combination with immunotherapy (IO), or IO alone, between September 2015 and March 2023. CONSORT diagram is available in Supplementary Fig. 1. Patients with AGAs (EGFR, n = 7 and ALK, n = 2), absence of remaining tumor tissue to assess AXL expression (n = 27) or pre-treated by non-palliative radiation and/or CT in the past year (n = 35) were excluded. Finally, we enrolled 89 patients with advanced NSCLC to assess the efficacy of the biomarker AXL in predicting response to IO in the original cohort (before propensity score matching). The median age of the patients was 64 years, with a range of 42 to 83 years. Among them, 43 patients (48.3 %) were 65 years or older. The median body mass index (BMI) was 23.4 kg/m^2 (table 1). The cohort included 55 males and 34 females. In terms of smoking history, 61 patients (68.5 %) were either never-smokers or former smokers, while 28 patients (31.5 %) were current smokers. Regarding PD-L1 expression, 50 patients (56.2 %) had a TPS < 50 % expression, 32 patients (36 %) had a TPS ≥ 50 %, and the PD-L1 status was unknown for 7 patients (7.9 %).

Histologically, the majority of patients had adenocarcinoma (64 patients, 71.9 %), followed by squamous cell carcinoma (22 patients, 24.7 %), and other subtypes (3 patients, 3.4 %). Most patients were at stage IV (84 patients, 94.4 %), with a small number at stages IIIA/IIIB (5 patients, 5.6 %).

Regarding treatment regimens, 52 patients (58.4 %) received CT alone, 14 patients (15.7 %) received IO alone, and 23 patients (25.8 %) were treated with a combination of IO and CT. Performance status, as measured by the PS-ECOG scale, showed that 78 patients (87.6 %) had a score of 0–1, while 11 patients (12.4 %) had a score of 2. Metastatic sites included the liver (7 patients, 7.9 %) and the CNS (22 patients, 24.7 %).

3.2. Clinical outcomes for patients treated by chemotherapy and/or immunotherapy in the original cohort according to AXL expression

In the original cohort, the superiority in terms of PFS was confirmed in favour of patients treated with IO +/- CT in comparison to patients treated by CT alone, with medians of 7.6 vs. 4.4 months ($p = 0.006$) (Supplementary Fig. 2A-B). Response rates also favoured the IO-treated group. In the CT group, 46 % (24/51) of cases showed disease progression at the first assessment. The objective response rate according to RECIST criteria was 22 % (11/49), and the disease control rate was 57 % (28/49). For the IO group, RECIST-assessable response was observed in 32 patients. Disease progression occurred in 32 % (10/31) cases at first assessment, while 2 patients achieved a complete response as the best response. The objective response and disease control rates were 48 % (15/31) and 64 % (20/31), respectively (Supplementary Fig. 2C).

AXL expression was positive (>1% TPS) in 47 % of cases (47/89), with values ranging from 0 % to 100 % and a median of 5 % (Fig. 1A-B). In the original cohort, AXL positivity (defined by TPS > 1 %) was associated with shorter PFS, with medians of 4.3 months for the AXL positive group and 5.3 months for the AXL negative group, $p = 0.044$ (Fig. 1C). There was no significant difference in OS ($p = 0.208$) (Fig. 1D).

We then analyzed patient survival according to both AXL status and the type of treatment received, differentiating between patients treated with IO and/or CT. PFS was significantly different ($p = 0.007$) (Fig. 1E). Pairwise comparisons revealed a significant difference between the IO-AXL negative group and the CT- AXL positive group ($p = 0.008$) and CT- AXL negative group ($p = 0.015$). No difference was noted among CT patients ($p = 1.00$). Similarly, no difference was found between IO-AXL positive patients and the CT group ($p = 0.988$). Finally, a trend was observed in favour of the IO-AXL negative group compared to IO-AXL positive patients ($p = 0.122$). Very similar results were observed in terms of overall survival (OS), with a survival benefit being noted only for patients in the IO-AXL negative group ($p = 0.018$) (Fig. 1F).

To confirm the clinical relevance of this AXL positivity threshold, we performed a cumulative ROC analysis based on the different levels of AXL expression observed. For both PFS and OS, we identified an optimal threshold at 1 % of positive tumor cells (Supplementary Fig. 3).

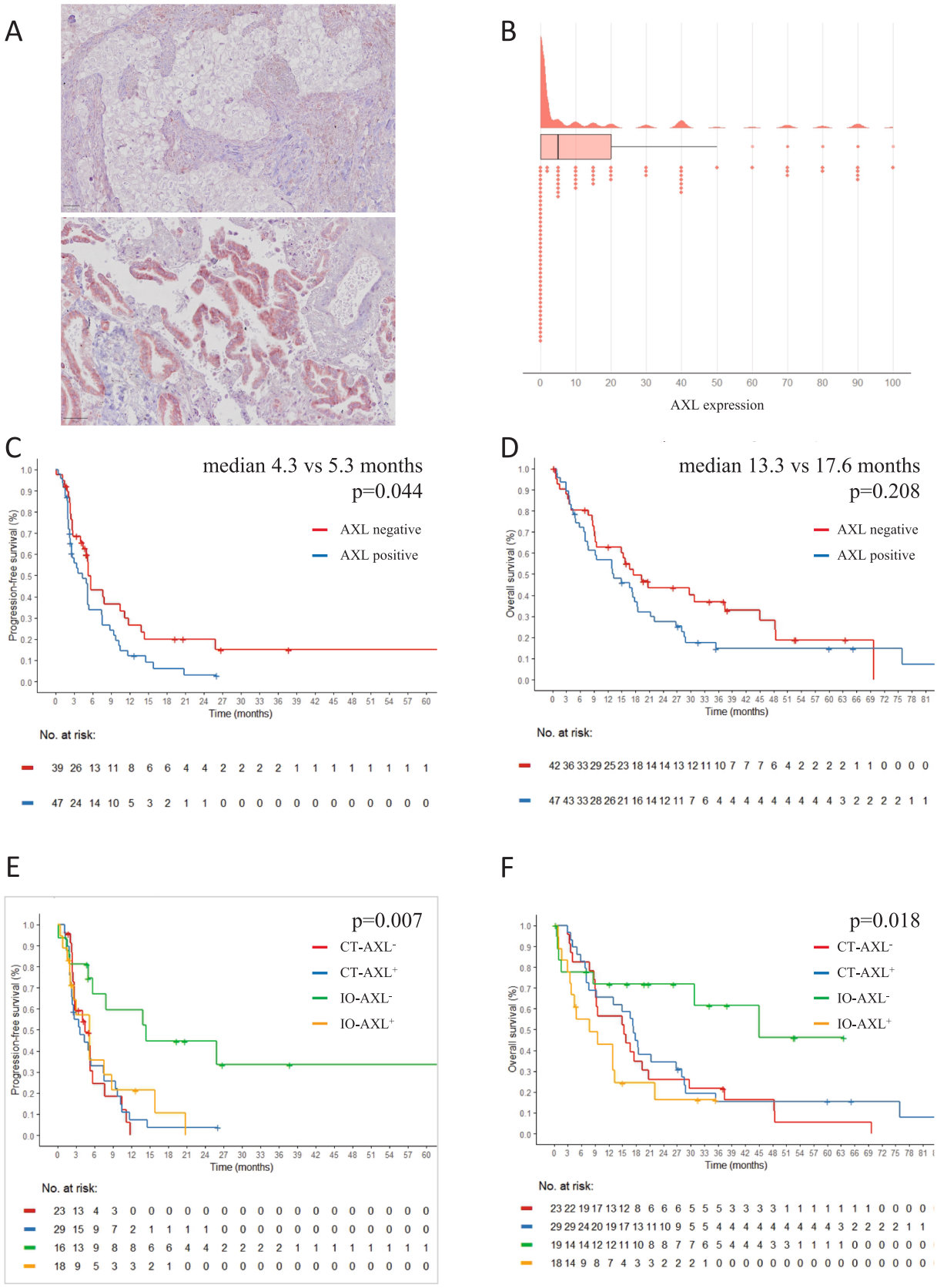

Fig. 1. Illustrations of NSCLC cases classified as AXL negative (upper image) and AXL positive (lower image). The scale bar represents 50 μm. The distribution of AXL expression is plotted in panel (B). Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) are shown in panels (C-D) and (E-F), respectively, for the global cohort. Survival curves are presented according to AXL expression and treatment groups: Chemotherapy (CT) and Immunotherapy (IO).

3.3. Clinical outcomes for patients treated by chemotherapy and/or immunotherapy in the propensity-matched cohort according to AXL expression

To account for potential prognostic factors imbalanced between the IO and CT groups, we then performed a propensity score matching. We included common prognostic factors, such as age, BMI, sex, PD-L1 expression, ECOG performance status, and the presence of brain metastases. Table 2 presents the characteristics of patients in the IO (n = 37) and CT (n = 52) groups before and after matching. Significant differences were observed before matching in various prognostic factors, such as age (p = 0.036), PD-L1 expression (p = 0.001), ECOG performance status (p = 0.025), and the presence of brain metastases (p = 0.005). After matching, 37 patients from the CT group were retained, with PD-L1 expression remaining the only statistically different factor (p < 0.01). Baseline characteristics by AXL status within each treatment arm are reported in Supplementary Tables S3 (CT) and S4 (IO). No significant differences were observed for age, BMI, sex, ECOG PS, histology, AJCC stage, smoking status, PD-L1 distribution, or metastatic sites (liver/CNS) between AXL-negative and AXL-positive patients in either arm.

We then confirmed the survival results observed in the initial cohort within the propensity-matched cohort. The results were similar, with better PFS in the IO-AXL negative group (p = 0.003) and no difference between AXL negative or positive patients treated with CT (Fig. 2A). Patients treated with IO and AXL positive seemed to have a response similar to those treated with CT alone. No differences were observed for patients treated with CT alone according to AXL expression. Similar results were observed for OS, favouring the IO-AXL negative group (Fig. 2B). In multivariate analysis, AXL expression was the only factor associated with shorter PFS (HR 4.15, 95 % CI 1.35–12.82, p = 0.013) (Fig. 2C). This finding was consistent with the multivariate analysis for OS (OS), where AXL expression had an HR of 5.634 (95 % CI 1.75–18.15, p = 0.004) (Fig. 2D). As expected, the presence of brain metastases was also associated with shorter OS (HR 7.23, 95 % CI 1.23–42.60, p = 0.029). A similar trend was observed for patients with a performance status of 2 (vs 0–1: HR 2.71, 95 % CI 0.73–10.0, p = 0.136) (Supplementary Tables 1).

In the original (unmatched) cohort, the difference in PFS between IO-treated patients with AXL-negative versus AXL-positive tumors did not reach statistical significance (log-rank p = 0.122; Fig. 1E). After 1:1 propensity score matching on age, BMI, sex, PD-L1 expression, ECOG performance status, and CNS metastases, the same comparison became significant (log-rank p = 0.003; Fig. 2A), indicating a clearer benefit from immunotherapy in AXL-negative tumors when baseline imbalances are reduced. This pattern was consistent for OS (Fig. 2B) and with multivariable Cox analyses in the matched cohort, where AXL positivity independently associated with shorter PFS (HR 4.15, 95 % CI 1.35–12.82, p = 0.013) and OS (HR 5.63, 95 % CI 1.75–18.15, p = 0.004; Fig. 2C–D; Supplementary Tables 1).

Thirty-one patients were evaluable according to RECIST criteria in the IO group, and thirty-four patients were evaluable in the CT group. Among patients in the CT group, 40 % (6/15) and 53 % (10/19) were in progression at the first assessment in the AXL negative and positive subgroups, respectively (data not shown). The response rates were 40 % (6/15) and 16 % (3/19), respectively (p = 0.14). The disease control rates were 60 % (9/15) and 47 % (9/19), respectively (p = 0.51; Fig. 3A). No complete response was observed. Among patients in the IO group, 14 % (2/14) and 29 % (5/17) were in progression at the first assessment in the AXL negative and positive subgroups, respectively. The response rates were 71 % (10/14) and 41 % (7/17), respectively (p = 0.15). The disease control rates were 85 % (12/14) and 58 % (10/17), respectively (p = 0.13; Fig. 3B). A complete response was observed in each IO sub-group (Fig. 3B).

Table 2
Clinicopathological characteristics comparisons before and after propensity score matching.

Characteristics		Before matching, n(%)			After matching, n(%)		
		CT alone (n = 52)	IO +/- CT (n = 37)	p-value	CT alone (n = 37)	IO +/- CT (n = 37)	p-value
Age (years)		63.5 [42–81]	67 [47–83]	**0.04**	64 [42–78]	67 [47–83]	0.11
Body mass index (kg/m^2)		23 [13.4–42.3]	23.5 [15.4–32.7]	0.50	22.4 [13.4–42.3]	23.5 [15.4–32.7]	0.61
Sex							
	Female	16 (30.8 %)	18 (48.6 %)	0.14	13 (35.1 %)	18 (48.6 %)	0.35
	Male	36 (69.2 %)	19 (51.4 %)		24 (64.9 %)	19 (51.4 %)	
Smoking history							
	Never / Former	32 (61.5 %)	29 (78.4 %)	0.15	14 (37.8 %)	29 (78.4 %)	0.203
	Current smokers	20 (38.5 %)	8 (21.6 %)		23 (62.2 %)	8 (21.6 %)	
PDL1 expression (TPS)							
	Negative*	29 (55.8 %)	7 (18.9 %)	**0.001**	20 (54.1 %)	7 (18.9 %)	**<0.01**
	Positive	23 (44.2 %)	30 (81.1 %)		17 (45.9 %)	30 (81.1 %)	
Histological sub-type							
	Non-squamous	36 (69.2 %)	31 (83.8 %)	0.19	24 (64.9 %)	31 (83.8 %)	0.11
	Squamous	16 (30.8 %)	6 (16.2 %)		13 (35.1 %)	6 (16.2 %)	
Stage **							
	IIIA/IIIB	4 (7.7 %)	1 (2.7 %)	0.59	4 (10.8 %)	1 (2.7 %)	0.35
	IV	48 (92.3 %)	36 (97.3 %)		33 (89.2 %)	36 (97.3 %)	
Regimen							
	CT alone	52 (100 %)	–	–	37 (100 %)	–	–
	IO +/- CT	–	37 (100 %)		–	37 (100 %)	
PS-ECOG							
	0–1	49 (94.2 %)	29 (78.4 %)	**0.03**	34 (91.9 %)	29 (78.4 %)	0.19
	2	3 (5.8 %)	8 (21.6 %)		3 (8.1 %)	8 (21.6 %)	
Metastatic sites							
	Liver metastasis	4 (7.7 %)	3 (8.1 %)	0.74	4 (10.8 %)	3 (8.1 %)	0.69
	CNS metastasis	19 (36.5 %)	3 (8.1 %)	**<0.01**	5 (13.5 %)	3 (8.1 %)	0.71

PDL1: Programmed Death-Ligand 1, TPS: tumor proportion score, CT; Chemotherapy, IO: Immunotherapy, PS-ECOG: Eastern Cooperative Oncology Group – Performance Status, CNS: central nervous system. Data are expressed as Median [range] or n(%), as appropriate. p-value was considered significant if < 0.05. * or unknown. ** Eighth Edition of the TNM Classification for Lung Cancer.

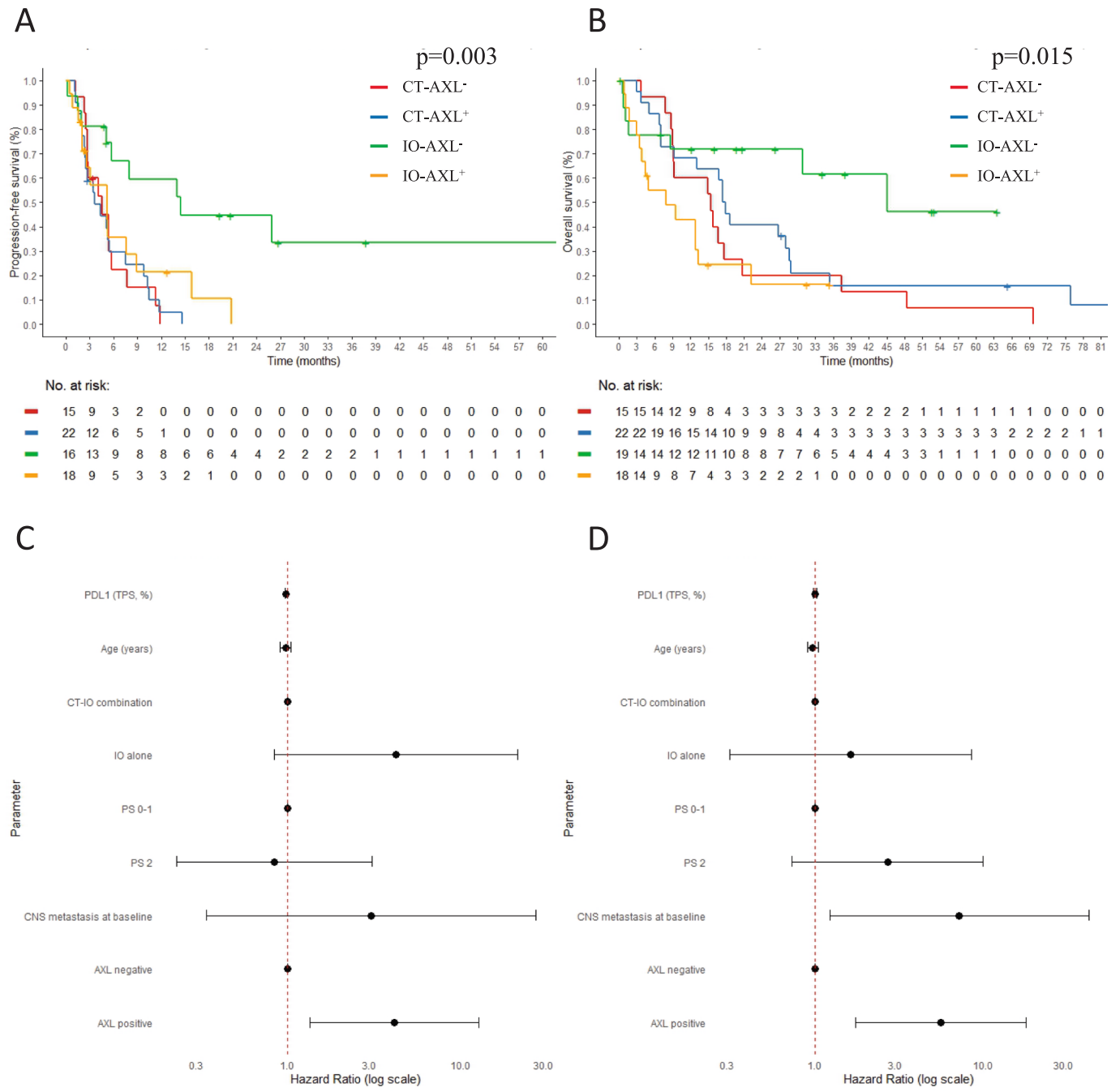

Fig. 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) OS (OS) in the propensity score-matched cohort according to AXL expression and treatment groups. Forest plot depicting factors associated with PFS (C) or OS in multivariate analysis. Note the emergence of a significant PFS difference between IO-AXL − and IO-AXL + after propensity matching (log-rank p = 0.003), whereas the same comparison showed only a non-significant trend in the original cohort (p = 0.122; Fig. 1E). CT: Chemotherapy; IO: Immunotherapy. PDLM1: Programmed Death Ligand 1; TPS: Tumor Proportion Score; PS: Performance Status; CNS: Central Nervous System.

3.4. Pathological and genomic profile associations with AXL expression

No significant associations were observed between AXL expression and clinicopathological characteristics. Especially, AXL did not differ statistically across PDL1 expression (p = 0.66), histological subtypes (p = 0.90), regimen of treatment (p = 0.48), or metastatic location (Supplementary Tables 2). NGS data were available for 45 cases of adenocarcinoma, regardless of the treatment received in the first line. In the overall population, KRAS mutations were the most frequently observed, occurring in 47 % of cases (21/45), including activating KRAS G12C mutation in 26 % of cases (12/45). STK11 mutations were the second most common alteration, identified in 31 % of cases (14/45), followed by CDKN2A mutations in 20 % of cases (9/45) (Fig. 4A). In subgroup analyses, KRAS G12C mutations were found in 17 % (4/23) of tumors with AXL negative status and 32 % (8/22) of tumors with AXL positive status. STK11 mutations were observed in 21 % (5/23) of AXL-negative tumors and 41 % (9/22) of AXL-positive tumors. BRAF mutations were observed in 9 % (2/23) of AXL-negative tumors and 18 % (4/22) of AXL-positive tumors (Fig. 4B).

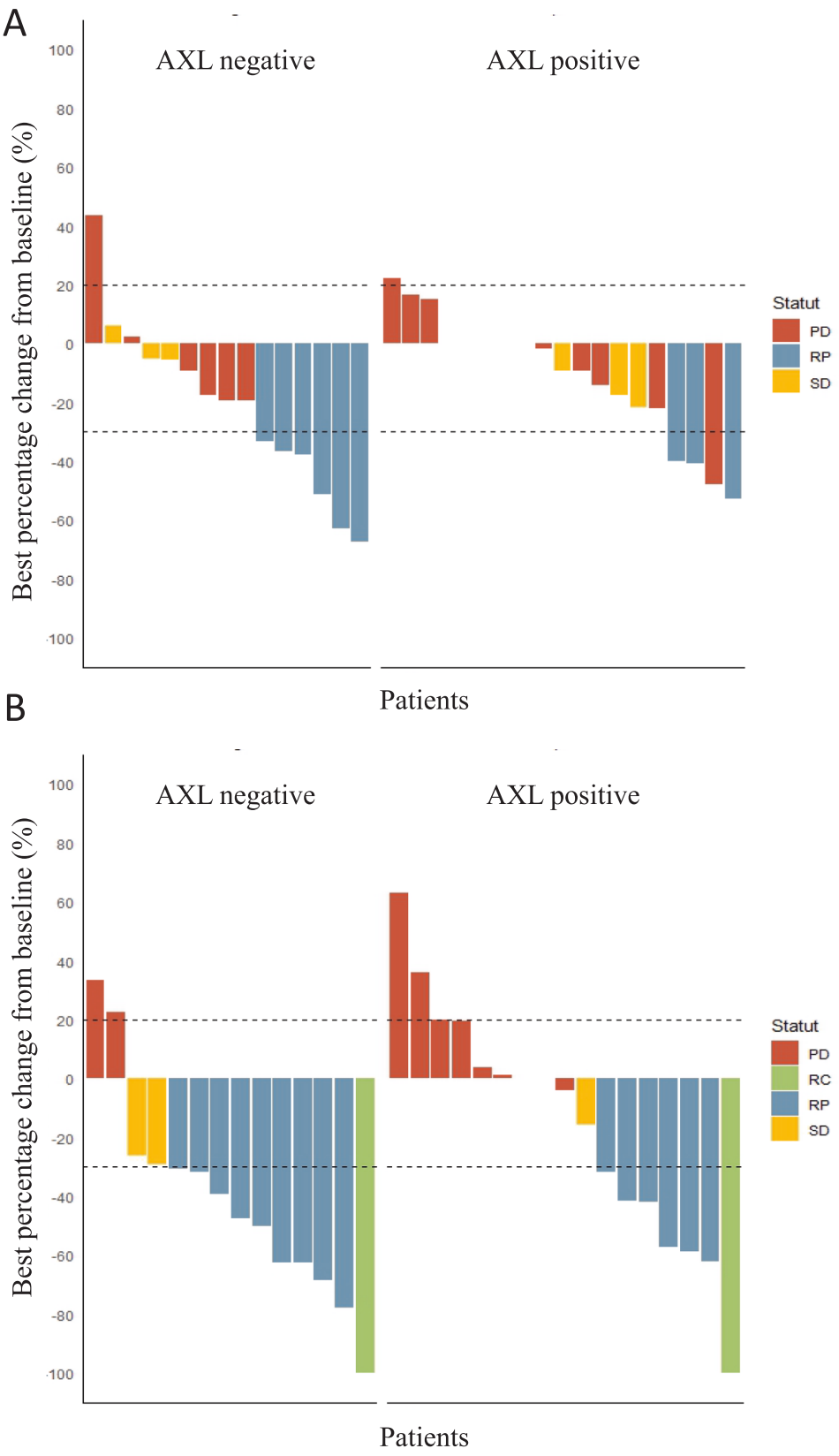

Fig. 3. Best Overall Responses in the propensity score-matched cohort. Waterfall plots show the best percentage change from baseline in target lesions for patients with at least one evaluable target lesion according to RECIST v1.1 criteria; data were available for 37 patients in the CT control group (A) 34 patients in the IO group (B). PD; Progressive Disease, RP: Partial Response; RC: Complete Response; SD: Stable Disease.

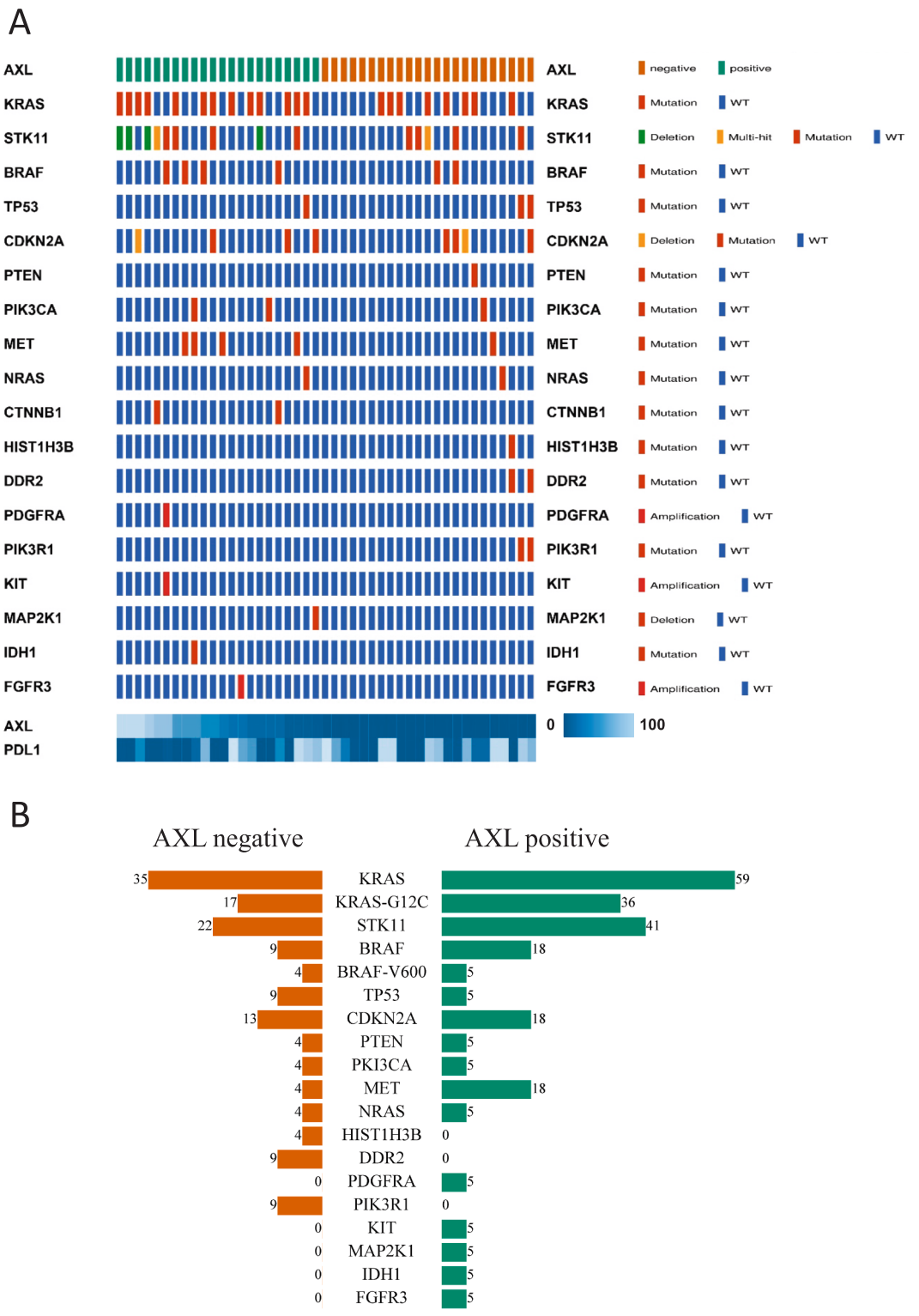

Fig. 4. Genomic landscape of NSCLC tumors according to AXL expression. (A) OncoPrint plot of the global original cohort demonstrating top recurrently altered genes. Both AXL and PDL1 are expressed by TPS. The heatmap is ordered according to increasing values of AXL expression. (B) Frequencies of most commonly altered genes according to AXL expression. PD-L1: Programmed death ligand-1.

4. Discussion

There is a pressing need for innovative strategies to improve the effectiveness of IO in clinical settings, as well as for predictive tools that can accurately identify IO responders based on the characteristics of their tumor microenvironment. To our knowledge, this is the first study demonstrating the predictive capabilities of AXL expression for first-line IO responses in metastatic NSCLC. Our study has several strengths,

including a cohort of 89 patients treated in the first line, controlled by a CT group, with a predictive effect specifically observed in the IO arm in terms of PFS and resulting in a significant OS benefit. These significant differences persisted after accounting for potential prognostic confounding factors through propensity score matching and multivariate analyses.

In NSCLC, it has been previously reported that AXL expression, evaluated by immunohistochemistry and using a cut-off of 25 % of tumor cells, was statistically associated with lymph node involvement ($p < 0.0001$) and the more advanced clinical stage ($p < 0.0001$) [19]. The reported difference with significance thresholds of 25 % and 0 % may be due, in part, to the fact that our study included only metastatic stages with a criterion focused on response to immunotherapy, whereas the study by Shieh et al. predominantly included non-metastatic patients with criteria based on TNM staging. A complementary study on surgically resected lung adenocarcinoma tissues ($n = 88$) evaluated mRNA and protein expression levels of both AXL and its ligand Gas6. Elevated levels of AXL mRNA/protein and Gas6 protein were significantly associated with poorer clinicopathological features and prognosis (5-year OS rates: AXL mRNA low: 72.3 %, high: 49.7 %, $p = 0.047$; AXL protein low: 77.5 %, high: 38.6 %, $p < 0.001$; Gas6 protein low: 70.5 %, high: 48 %, $p = 0.042$). Conversely, higher Gas6 mRNA expression correlated with better clinicopathological features and prognosis (5-year OS rates: Gas6 mRNA low: 59.2 %, high: 81.8 %, $p = 0.054$). Multivariate analysis indicated that high AXL mRNA expression could be an independent factor for poorer prognosis ($p = 0.04$) [20]. Comparing the thresholds used for this report for AXL quantification is not feasible with our study, as Masashi et al. employed a composite IHC score that integrates both staining intensity and the percentage of positive cells.

Considering resistance to treatment, AXL has been suggested as both a marker and a mechanism of resistance across various cancer types. Specifically, AXL has been recognized as a key factor in mediating drug resistance in ovarian cancer cell lines resistant to cisplatin [21]. In a comprehensive analysis of 643 human cancer cell lines, AXL was strongly linked to a drug-resistant mesenchymal phenotype. Moreover, the inhibition of AXL showed a particularly synergistic effect when combined with antimitotic drugs like docetaxel [22]. AXL has been demonstrated to play a role in resistance to a range of cytotoxic agents, radiation, and various targeted therapies [23]. In metastatic NSCLC with EGFR mutations, AXL expression has been described as a mechanism of resistance to EGFR TKIs [24,25]. Previous research has identified associations between AXL expression and resistance to various targeted therapies in NSCLC, including ALK, PARP, and VEGF/VEGFR-related therapies [26–29].

Numerous studies indicate that AXL may be involved in resistance to IO. The TAM receptor superfamily, consisting of TYRO3, AXL, and MERTK, plays a crucial role in maintaining tissue and immune homeostasis [30]. Dysregulation of TAM receptor signalling has been linked to a range of diseases, including cancer, fibrosis, and viral infections. For example, TAM receptors are involved in epithelial-to-mesenchymal transition (EMT), maintaining stem cell phenotypes, immune modulation, proliferation, angiogenesis, and resistance to both conventional and targeted therapies [31,32]. EMT has already been reported as a mechanism of resistance to various drugs and therapeutic strategies in NSCLC [15]. Upon binding with its ligand GAS6, AXL modulates cell signalling pathways and facilitates communication between different elements of the tumor microenvironment, such as cancer cells, endothelial cells, and immune cells.

Accumulating evidence suggests that AXL is a promising molecular target for addressing therapy resistance and immunosuppression, with AXL inhibitors showing the potential to enhance the effectiveness of immune checkpoint inhibitors [17]. Additionally, we observed that STK11 mutations appeared to be more common in AXL-positive tumors. It has been previously reported that the presence of a STK11 mutation was associated with a negative prognosis [33]. These factors collectively support that tumors expressing AXL may be less responsive to IO, as suggested by our data.

We explicitly observed a shift from a non-significant trend in the unmatched cohort to a significant PFS difference in the propensity-matched cohort, favouring IO-treated patients with AXL-negative tumors. This change likely reflects the reduction of confounding by baseline prognostic factors (age, ECOG PS, CNS metastases, PD-L1, BMI) achieved through matching. Of note, while PD-L1 remained imbalanced between treatment groups at the cohort level after matching, within-arm comparisons by AXL status showed broadly similar distributions of baseline characteristics. Together with the multivariable Cox results in the matched set, these findings support that AXL status is independently associated with reduced IO benefit, rather than merely capturing general prognosis.

Although AXL has been implicated in chemoresistance across several tumor models and drug classes (including antimitotic) [21–23], we did not observe clinically meaningful differences in the activity of standard first-line platinum-based doublets according to AXL status in metastatic NSCLC. Several, non-exclusive explanations are plausible. AXL-driven resistance appears context- and regimen-specific: the strongest preclinical signals have been described with antimitotic agents (e.g., docetaxel) and in pronounced EMT states [22], whereas our real-world first-line cohort predominantly received platinum + pemetrexed or platinum + taxane, where AXL may play a more limited role at clinical scale. Cytotoxic efficacy in NSCLC is strongly also influenced by pathways orthogonal to AXL/EMT (e.g., nucleotide metabolism for pemetrexed, DNA-damage response for platinum) and by co-mutations such as KRAS, STK11, or KEAP1, which may dominate over any modest AXL effect. Furthermore, our assay quantified total AXL protein by IHC but did not capture AXL activation (phosphorylation), ligand (GAS6) availability, or microenvironmental AXL on immune/stromal cells, which may affect chemotherapy response. Finally, the sample size and backbone heterogeneity of the CT arm reduce statistical power to detect small effect sizes. By contrast, the association between AXL negativity and improved immunotherapy outcomes observed here is biologically congruent with AXL's role in EMT-linked immune escape and TAM-receptor–mediated immunosuppression [17,31,32], suggesting that AXL may act primarily as a predictive marker for IO benefit rather than a universal determinant of cytotoxic chemotherapy response in NSCLC. Prospective, regimen-stratified studies with standardized AXL/ phospho-AXL assays and broader genomic adjustment are warranted to clarify these relationships.

This study has several limitations. First, it is a retrospective, single-center analysis, which may introduce selection and information biases. Second, the overall sample size is modest, and the four-cell comparison across treatment and biomarker strata (CT-AXL−/CT-AXL+, IO-AXL−/IO-AXL +) has limited power. Consequently, some analyses were primarily descriptive and effect estimates carry wide confidence intervals. Third, despite propensity-score matching, PD-L1 expression remained imbalanced between groups, reflecting real-world treatment allocation (e.g., IO monotherapy in PD-L1 $\geq$ 50 %); therefore, residual confounding cannot be excluded. Additionally, NGS data were available only in a subset, and STK11 mutations were more frequent in AXL-positive tumors, potentially contributing to poorer outcomes in this subgroup. As a result, we were unable to adjust for STK11 (or other co-mutations) in the full multivariable models. Finally, AXL assessment relied on a single IHC antibody and a predefined TPS cut-off; external validation with standardized pre-analytical conditions is warranted. Collectively, these constraints underscore the need for larger, prospective, multicenter studies with comprehensive genomic annotation to confirm the predictive value of AXL for IO benefit in metastatic NSCLC.

Given that patients with NSCLC expressing AXL exhibit significantly less benefit from IO, this approach could help better identify those who are suitable candidates for this treatment. It could also prevent unnecessary exposure of patients to a combination of CT and IO, which is associated with an increased risk of toxicity. Furthermore, AXL is a receptor tyrosine kinase that is targetable with emerging inhibition

strategies, including both tyrosine kinase inhibitors (TKIs) and blocking antibodies [23]. For example, a phase II trial investigated the use of Bemcentinib (BGB324), a highly selective AXL inhibitor, in combination with IO (i.e. pembrolizumab) for patients with advanced NSCLC [34]. Among 29 patients assessable for a response, 7 achieved a partial response, yielding a response rate of 24 %. In patients with AXL-positive tumors, the objective response rate was 40 %. Of the 5 responders for whom PD-L1 status was known, 4 (80 %) were either PD-L1 negative or had low PD-L1 expression. During stage 1 of the trial, the median PFS was 4.0 months (95 % CI 1.9 – NR) overall, and 5.9 months for AXL-positive patients (n = 10; 3.0 – NR). Targeting AXL could thus be a valuable strategy for patients, particularly in combination with IO, to prevent immune escape.

5. Conclusion

We demonstrate for the first time that tumor expression of AXL is associated with a lack of benefit from immunotherapy compared to chemotherapy alone in the first-line treatment of metastatic NSCLC without targetable oncogenic addiction. AXL expression could serve as a biomarker to identify patients who would benefit from the addition of immunotherapy to their treatment regimen, and it may also act as a therapeutic target to restore sensitivity to immune checkpoint inhibitors. Further clinical studies are needed to fully assess the clinical relevance of this biomarker to allow better patient selection and optimal clinical management.

6. Funding information

With financial support from ITMO Cancer of Aviesan within the framework of the 2021–2030 Cancer Control Strategy, on funds administered by Inserm, URCA and with financial support from the Amgen France Fund for Science and Humanity.

CRediT authorship contribution statement

Julien Ancel: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Maxime Dewolf:** Writing – original draft, Visualization, Validation, Resources, Data curation. **Béatrice Nawrocki-Raby:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Anne Durlach:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Véronique Dalstein:** Writing – review & editing, Supervision, Investigation, Formal analysis. **Nathalie Lalun:** Writing – review & editing, Methodology, Investigation. **Valérian Dormoy:** Writing – review & editing, Visualization, Validation, Supervision, Methodology. **Gaëtan Deslée:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Christine Gilles:** Writing – review & editing, Visualization, Validation, Supervision, Methodology. **Myriam Polette:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JA reports participation in advisory boards and support for attending meetings from Roche, Pfizer, MSD, Bristol-Myers Squibb, Novartis, AstraZeneca, Takeda, Sanofi, and Amgen, outside of the submitted work. MD reports participation in advisory boards and support for attending meetings from Roche, Pfizer, MSD, Bristol-Myers Squibb, AstraZeneca, Chugai, Sanofi, and Amgen, outside of the submitted work. VDo reports support for attending meetings from AstraZeneca. GD reports participation in advisory boards and support for attending meetings from Chiesi, AstraZeneca, GSK, and Sanofi.

Acknowledgments

The research effort associated with this article was funded in part by the “Partenariat Hubert Curien-Tournesol”.

Authors’ contributions

AJ: conceptualization, software, methodology, formal analysis, visualization, writing original draft, writing–review, editing and he is the guarantor of this study. MD: conceptualization, writing–review, visualization and editing. BNR: writing–review, visualization and editing. VDa: writing–review, visualization and editing. VDo: writing–review, visualization and editing. NL: writing–review, visualization and editing. AD: writing–review, visualization and editing. GD: conceptualization, visualization, writing original draft, writing–review, editing. CG: conceptualization, visualization, writing original draft, writing–review, editing. MP: conceptualization, methodology, formal analysis, visualization, writing original draft, writing–review, editing.

Ethics approval and consent to participate

This retrospective observational study was approved by the University Hospital of Reims’ data protection departments (MR004160420221). Information notices for non-opposition were sent to patients living at the time of data collection, in accordance with French law.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108853.

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