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The Prognostic & Predictive Role of ATM Expression in Patients with Metastatic Non-Small Cell Lung Cancer Receiving Pembrolizumab Monotherapy or Combination with Chemotherapy

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Abstract: Background/Objectives: This study investigated the prognostic and predictive significance of ATM expression in metastatic non-small cell lung cancer (NSCLC) patients treated with pembrolizumab. **Methods:** A retrospective analysis was conducted on 49 patients with metastatic NSCLC who received first-line pembrolizumab, either as a single agent or combined with chemotherapy. ATM expression in archival pathology specimens was assessed using immunohistochemistry. Nuclear staining was considered positive. ATM expression was categorized into low and high groups based on staining intensity and percentage of positive cells. Subsequently, the prognostic and predictive value of ATM expression was evaluated. **Results:** The median age was 64 years (range, 45-81). Most patients (91.8%) were male, and the majority (75.5%) had adenocarcinoma. The objective response rate (ORR) was 69.4%. ATM expression was high in 75.5% of patients. Patients with low ATM expression had significantly longer progression-free survival (PFS) compared to those with high expression (51 vs. 5.7 months, P = 0.004). In multivariate analysis, ATM expression was the only independent prognostic factor for PFS. Moreover, patients with high ATM expression had significantly shorter overall survival (OS) compared to those with low expression (51 vs. 8.9 months, P = 0.013), which was statistically significant in multivariate analysis (HR 2.48, p = 0.041). Logistic regression analysis showed that ATM expression was significantly associated with response to treatment (p = 0.006; OR: 0.16, 95% CI: 0.08-0.48), as were the presence of bone metastasis and absence of liver metastasis. **Conclusions:** Lower ATM expression was associated with better prognosis and pembrolizumab treatment response, suggesting that ATM expression may be a valuable biomarker for predicting disease progression and treatment response.

Keywords: non-small cell lung cancer; ATM expression; pembrolizumab; progression-free survival; overall survival

1. Introduction

ATM (ataxia-telangiectasia mutated), encoded by the ATM gene, is a protein kinase involved in DNA damage repair. It plays a crucial role in the cellular response to double-strand DNA breaks (DSBs). When the MRE11-RAD50-NBS1 (MRN) complex detects a DSB, it activates ATM, which then phosphorylates downstream proteins to trigger DNA repair, cell cycle checkpoints, or apoptosis [1]. The critical role of ATM lies in preserving genomic integrity by preventing DNA mutations that contribute to tumor formation and progression. Between 0.2% and 0.7% of the population carries pathogenic germline ATM gene variants, particularly those that result in a truncated protein, which increases susceptibility to breast, ovarian, and pancreatic cancer [2]. Lung cancer patients exhibit a slightly elevated rate of inherited ATM gene mutations (up to 1.2-1.9%) compared to the general population, with this increase being most noticeable in lung adenocarcinoma (LUAD) [3,4].

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ATM is often somatically mutated in lung tumors, in addition to germline variants. The Cancer Genome Atlas (TCGA) cohorts reveal that ATM is the most frequently mutated DNA damage response gene in NSCLC, with mutation rates around 9% in LUAD and 4% in lung squamous cell carcinoma [5,6]. The pattern of ATM mutations differs from that of common oncogenes; instead of being confined to specific areas, they are dispersed across the entire 150 kilobase gene [7]. The high frequency of germline and somatic ATM gene variants in non-small cell lung cancer suggests their potential as prognostic biomarkers and/or predictors of therapeutic response.

Through next-generation sequencing (NGS) analysis of 5,172 NSCLC tumors (using OncoPanel or MSK-IMPACT), Ricciuti et al. found that 9.7% of cases had damaging ATM mutations [8]. Factors linked to ATM mutations included being female, having a history of smoking, non-squamous lung cancer, a high tumor mutation burden (TMB), and PD-L1 positivity [8]. ATM-mutant tumors were more likely to also have KRAS, STK11, KMT2D, and KEAP1 mutations, but less likely to have TP53 and EGFR mutations [8]. Vokes et al. studied ATM mutations in a significantly larger NSCLC group (N = 26,857), combining data from five separate clinical and genomic databases [9]. Vokes et al. found that 11.2% of NSCLC cases had non-synonymous ATM mutations, confirming that these mutations are linked to KRAS mutations and high TMB, inversely linked to TP53 and EGFR mutations, and more common in lung adenocarcinoma and patients with a smoking history [9].

Understanding the effects of the identified ATM mutations on protein production was a goal of both research groups, who utilized immunohistochemistry (Ricciuti) and reverse-phase protein arrays (Vokes) to analyze protein expression [8,9]. Predictably, ATM protein was less abundant in tumors with truncating mutations (like frameshifts or nonsense mutations) than in those with missense mutations.

Finally, to determine the impact of ATM mutations on patient outcomes, both studies performed correlation analyses. Ricciuti et al. discovered that while ATM mutations alone didn't influence survival or immunotherapy response, patients with both ATM and TP53 mutations had better PFS after immunotherapy [8]. Conversely, Vokes et al. found that patients with functionally significant ATM mutations (such as truncating, splice site, or specific missense mutations) had improved OS, and that ATM-mutant patients specifically benefited from chemoimmunotherapy, showing better survival rates (9). Despite the discrepancies in reported links between ATM status and patient outcomes, both studies highlighted potential prognostic associations that require additional research.

In our study, we aimed to reinvestigate the prognostic and predictive significance of ATM expression in metastatic NSCLC patients treated with pembrolizumab alone or combined with chemotherapy (CT).

2. Materials and Methods

This study, conducted at Istanbul Medipol University between 2022 and 2024, included 49 metastatic NSCLC patients (over 18 years old, no actionable driver mutations) who received first-line pembrolizumab monotherapy or pembrolizumab with platinum chemotherapy.

The study included patients with enough tumor tissue for ATM and PD-L1 re-evaluation. Patients with poor performance status (ECOG PS 3/4) and those lost to follow-up were excluded from analysis.

Patient clinical data were gathered retrospectively from their medical records. Data on baseline characteristics such as age, gender, smoking history, histopathological type, stage of disease at diagnosis, history of curative intent therapy, T stage, presence of liver, brain, and bone metastases, PD-L1 status, first-line treatment, and ATM score were recorded after obtaining written informed consent from patients or their relatives. PD-L1 expression was determined using the PD-L1 IHC 22C3 pharmDx assay (Agilent), and results were categorized based on the tumor proportion score.

Immunohistochemistry targeting ATM was conducted on whole-tissue sections of biopsies containing tumors, including tru-cut biopsies and tumor samples from resection materials. To this end, 2 μm thick sections were prepared from paraffin-embedded blocks. Automated immunohistochemistry for ATM (using a rabbit polyclonal antibody at 1:250 dilution, SANTA CRUZ, G12) was performed on a BenchMark ULTRA staining instrument (Ventana Medical Systems,

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Tucson, AZ) for all cases. Antibody clone was applied with the UltraView DAB IHC Detection Kit, following the manufacturer's instructions. Positive external controls were included on each slide. Nuclear staining was considered positive.

The percentage of ATM-positive cells and staining intensity were scored. Intensity was graded as: negative, 0; weak, 1; moderate, 2; or strong, 3. The percentage of positive cells was graded as: 0, <5%; 1, 5%-25%; 2, 26%-50%; 3, 51%-75%; and 4, >75%. These two measurements were multiplied to obtain weighted scores ranging from 0-12, and cases were categorized into low expression group (score range: 0-5) and high expression group (score range: 6-12) (Figures 1 and 2).

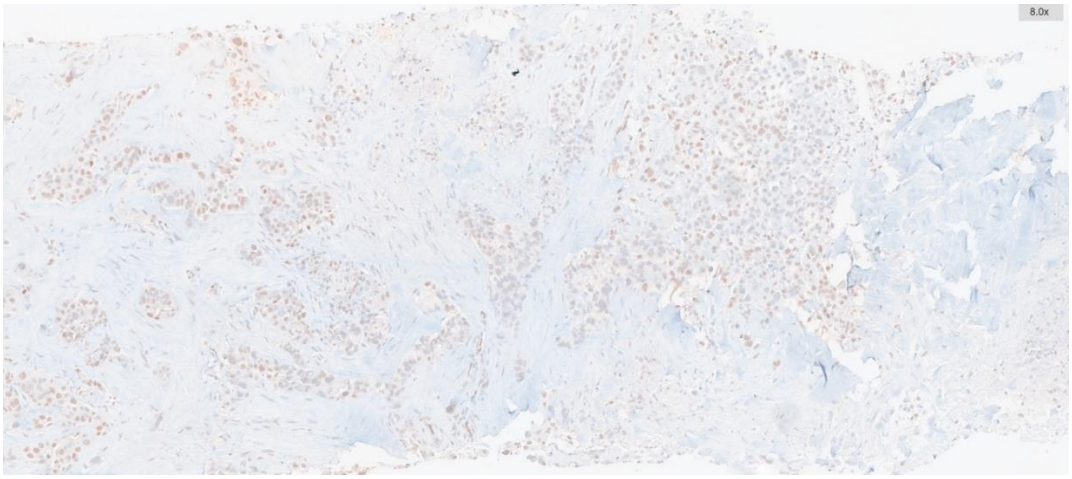

Figure 1. ATM positivity with low expression (1+ nuclear staining is present in 20% of tumor cells).

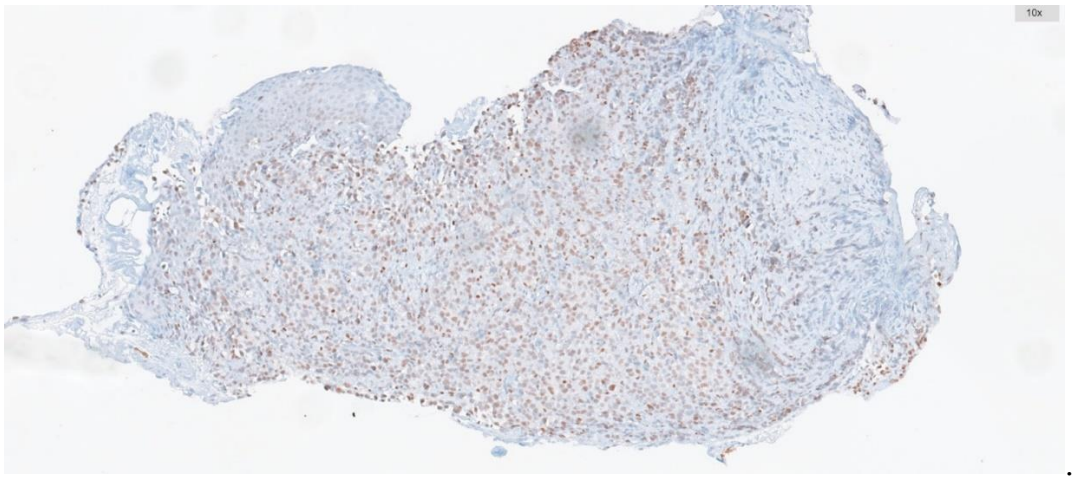

Figure 2. ATM positivity with high expression (2+ nuclear staining is present in 90% of tumor cells).

All statistical analyses were conducted using IBM SPSS Statistics 22.0. Baseline characteristics were described using descriptive statistics, survival analysis was performed with Kaplan-Meier curves, and the log-rank test was used for comparisons. The prognostic impact of clinicopathological features was evaluated through univariate analysis. Subsequently, Cox proportional hazards regression was used in multivariate analysis to determine independent prognostic factors for PFS and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated and reported. Additionally, multivariate logistic regression was used to identify independent predictors of treatment response. Results are presented as odds ratios (ORs) with 95% CIs. Data are shown as mean (SD), median (range), 95% CI, or percentages, as applicable. A two-sided p-value of < 0.05 was considered statistically significant.

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3. Results

Between 2022 and 2024, forty-nine patients over the age of 18 with metastatic NSCLC who had no actionable driver mutation were included in this study at the Istanbul Medipol University Department of Medical Oncology. All patients received pembrolizumab monotherapy or pembrolizumab plus platinum doublet chemotherapy in the first-line setting.

Patients who had sufficient tumor tissue for reassessing ATM and PD-L1 expression were included. Patients with ECOG PS 3/4 who were not candidates for systemic treatment and patients with loss of follow-up were excluded from the data analysis.

The clinical features of the patients were obtained retrospectively from medical records. Data on baseline characteristics such as age, gender, smoking history, histopathological type, stage of disease at diagnosis, history of curative intent therapy, T stage, presence of liver, brain, and bone metastases, PD-L1 status, first-line treatment, and ATM score were recorded after obtaining written informed consent from patients or their relatives. PD-L1 expression was assessed by PD-L1 IHC 22C3 pharmDx assay (Agilent) and expressions were categorized according to the tumor proportion score.

Immunohistochemistry targeting ATM was conducted on whole-tissue sections of biopsies containing tumors, including tru-cut biopsies and tumor samples from resection materials. To this end, 2 µm thick sections were prepared from paraffin-embedded blocks. Automated immunohistochemistry for ATM (using a rabbit polyclonal antibody at 1:250 dilution, SANTA CRUZ, G12) was performed on a BenchMark ULTRA staining instrument (Ventana Medical Systems, Tucson, AZ) for all cases. Antibody clone was applied with the UltraView DAB IHC Detection Kit, following the manufacturer's instructions. Positive external controls were included on each slide. Nuclear staining was considered positive.

The percentage of ATM-positive cells and staining intensity were scored. Intensity was graded as: negative, 0; weak, 1; moderate, 2; or strong, 3. The percentage of positive cells was graded as: 0, <5%; 1, 5%-25%; 2, 26%-50%; 3, 51%-75%; and 4, >75%. These two measurements were multiplied to obtain weighted scores ranging from 0-12, and cases were categorized into low expression group (score range: 0-5) and high expression group (score range: 6-12) (Figures 1 and 2).

Table 1. Tumor and patients characteristics according to ATM expression.

Clinicopathological features	ATM Low expression n (%)	ATM High expression n (%)	p value
Age, years			0.49
≤60	15 (40.5)	3 (25.0)	
>60	22 (59.5)	9 (75.0)	
Gender			0.04
Female	1 (2.7)	3 (25.0)	
Male	36 (97.3)	9 (75.0)	
Smoking History			0.34
Never	3 (8.1)	2 (16.7)	
Current	20 (54.1)	8 (66.7)	
Former	14 (37.8)	2 (16.7)	
Histopathological type			0.16
Adenocarcinoma	30 (81.1)	7 (58.3)	
Squamous cell carcinoma	6 (16.2)	5 (41.7)	
Nos	1 (2.7)	0 (0.0)	
Initial metastatic			0.23
Yes	31 (83.8)	8 (66.7)	
No	6 (16.2)	4 (33.3)	
Curative Surgery			0.62
Yes	4 (10.8)	2 (16.7)	
No	33 (89.2)	10 (83.3)	

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Curative CRT			0.25
Yes	2 (5.6)	2 (16.7)	
No	34 (94.4)	10 (83.3)	
T Stage			0.39
T1	13 (35.1)	2 (16.7)	
T2	11 (29.7)	3 (25.0)	
T3	6 (16.2)	2 (16.7)	
T4	7 (18.9)	5 (41.7)	
Liver Metastases			0.66
Present	6 (16.2)	3 (25.0)	
Absent	31 (83.8)	9 (75.0)	
Brain metastases			0.73
Present	12 (32.4)	3 (25.0)	
Absent	25 (67.6)	9 (75.0)	
Bone metastases			1.0
Present	20 (54.1)	6 (50.0)	
Absent	17 (45.9)	6 (50.0)	
PD-L1 Status (TPS)			0.90
<%1	3 (8.1)	1 (8.3)	
%1-50	15 (40.5)	4 (33.3)	
>%50	19 (51.4)	7 (58.3)	
First line treatment			1.0
Pembrolizumab monotherapy	7 (18.9)	2 (16.7)	
Pembrolizumab plus platin doublet	30 (81.1)	10 (83.3)	

*TPS: Tumor Proportion Score CRT: Chemoradiotherapy.

The objective response rate (ORR) was 69.4%. ATM expression was high in 37 patients (75.5%) and low in 12 patients (24.5%). With a median follow-up of 25.5 months, the median PFS was significantly longer in patients with low ATM expression compared to those with high expression (51 months vs. 5.7 months, P = 0.004) (Figure 3). In multivariate analysis, only ATM expression was an independent prognostic factor for PFS (Table 2). On the other hand, the median OS was significantly shorter in patients with high ATM expression compared to those with low expression (51 months vs. 8.9 months, p = 0.013) (Figure 4). Multivariate analysis for OS identified ATM expression as the only independent prognostic factor (HR 2.48, P = 0.041) (Table 3).

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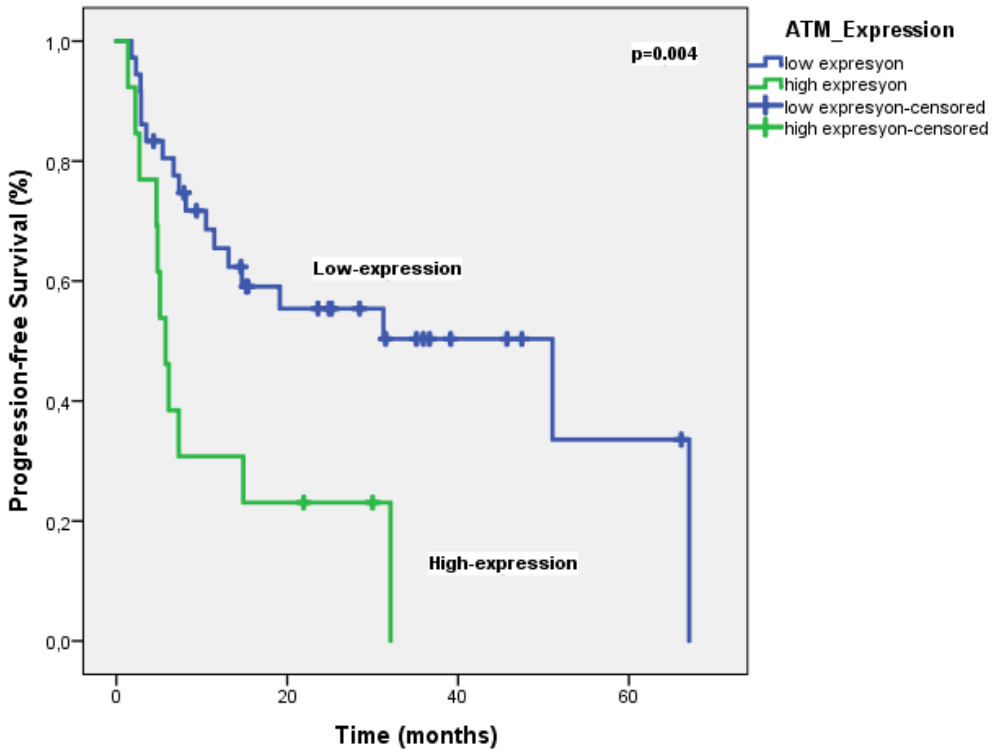

Figure 3. Proggression-free survival curves according to the ATM expression.

Table 2. Univariate and multivariate analysis results for PFS.

Variable	Median PFS (months)	Univariate p value	HR (%95 CI)	Multivariate p value
Age, years		0.23		
≤60	31.2			
>60	10.5			
Gender		0.03	0.60 (0.17-2.12)	0.43
Female	6.1			
Male	31.2			
Initial metastatic		0.44		
Yes	13.1			
No	19.3			
Curative Surgery		0.19		
Yes	51.0			
No	11.4			
T Stage		0.44		
T1	51.0			
T2	14.8			
T3	8.1			
T4	5.4			
Liver Metastases		0.26		
Present	10.5			
Absent	19.1			
Bone metastases		0.11		
Present	11.4			
Absent	51.0			
PD-L1 Status (TPS)		0.66		
<%1	8.13			

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%1-50	13.1			
>%50	19.1			
First line treatment		0.15	1.88 (0.62-5.66)	0.26
Pembrolizumab monotherapy	51.0			
Pembrolizumab plus platin doublet	13.1			
ATM Score		0.004	2.49 (1.07-5.76)	0.033
Low expression	51.0			
High expression	5.7			
Site of metastasis		0.38	0.91 (0.63-1.32)	0.64
Liver	7.3			
Brain	32.1			
Bone	11.4			

*TPS: Tumor Proportion Score.

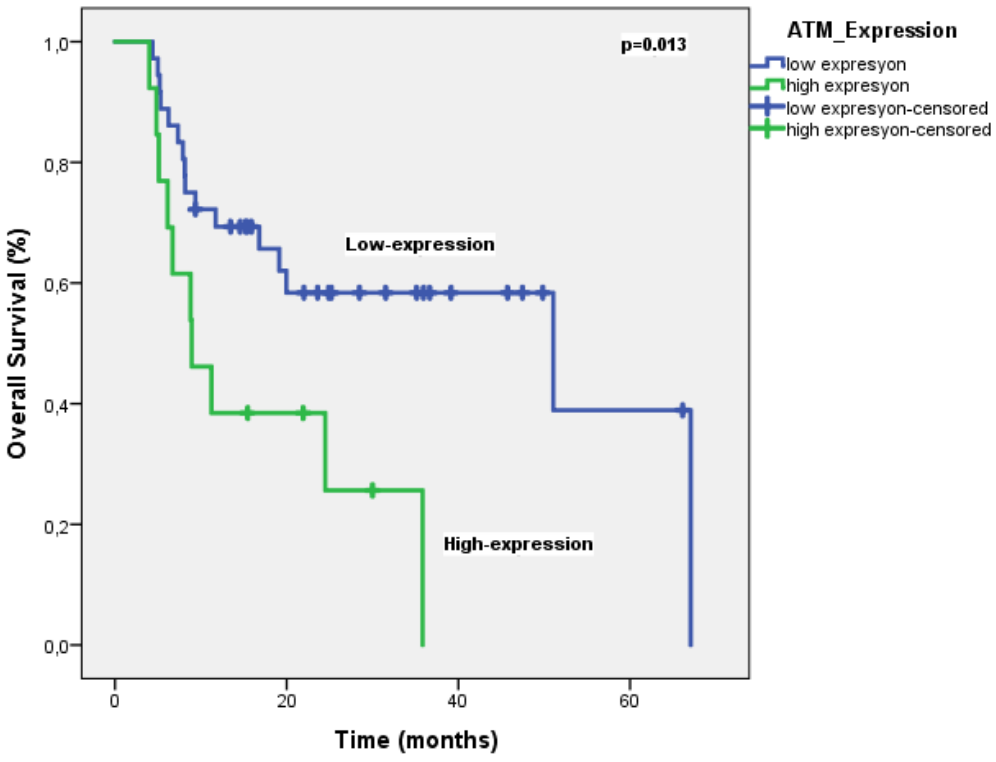

Figure 4. OS curves according to the ATM expression.

Table 3. Univariate and multivariate analysis results for OS.

Variable	Median OS (months)	Univariate p value	HR (%95 CI)	Multivariate p value
Age, years		0.29		
≤60	35.8			
>60	19.1			
Gender		0.16	0.75 (0.19-2.94)	0.68
Female	8.1			
Male	35.			
Initial metastatic		0.42		

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Yes	19.9			
No	51.0			
Curative Surgery		0.30		
Yes	51.0			
No	19.9			
T Stage		0.13		
T1	51.0			
T2	67.0			
T3	19.1			
T4	7.9			
Liver Metastases		0.81		
Present	35.8			
Absent	24.5			
Bone metastases		0.55		
Present	19.9			
Absent	51.0			
PD-L1 Status (TPS)*		0.59		
<%1	9.36			
%1-50	35.8			
>%50	19.1			
First line treatment		0.30	1.61 (0.52-4.95)	0.40
Pembrolizumab monotherapy	51.0			
Pembrolizumab plus platin doublet	24.5			
ATM Score		0.013	2.48 (1.03-5.94)	0.041
Low expression	51.0			
High expression	8.9			
Site of metastasis		0.90	1.09 (0.72-1.63)	0.67
Liver	NR*			
Brain	35.83			
Bone	19.96			

*TPS: Tumor Proportion Score NR: Not Reached.

Logistic regression analysis revealed that ATM expression is a significant predictor of treatment response in patients with metastatic NSCLC receiving pembrolizumab-based therapy**.** In other word, patients with high ATM expression had a significantly lower likelihood of responding to treatment (OR: 0.06, p=0.006, 95% CI: 0.08-0.48). In contrast, gender, first-line treatment type, and brain metastases were not associated with treatment response. However, liver and bone metastases were significantly linked to a higher likelihood of treatment response (OR: 26.65, p=0.023 95%CI 1.58-447 and OR: 10.99, p=0.031 95% CI 1.25-96.7 respectively) (Table 4). These findings highlight the potential importance of ATM expression as a biomarker for predicting treatment outcomes in NSCLC.

Table 4. Predictors of First-Line Pembrolizumab Response in Metastatic NSCLC.

Factors	Coefficient ß	Wald X^2	p	OR	95% CI
ATM Score (low vs high)	-2.80	7.42	0.006	0.06	0.008-0.45
Gender	-0.14	0.003	0.95	0.86	0.007-109
1st line treatment	-1.74	2.12	0.14	0.17	0.017-1.81
Liver metastasis	3.28	5.20	0.023	26.65	1.58-447
Brain metastasis	1.47	1.97	0.16	4.38	0.55-34.5
Bone metastasis	2.39	4.67	0.031	10.99	1.25-96.7

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4. Discussion

Multiple studies have confirmed that NSCLC is often characterized by DNA repair deficiencies caused by ATM mutations [10–12]. Two recent investigations found that ATM deficiency in lung adenocarcinomas occurs in 18% to 40% of cases [13,14]. In our study, 75.5% of patients exhibited high ATM expression, suggesting that alterations in ATM are common in NSCLC. Petersen and colleagues identified the ATM expression index (ATM-EI) as a significant prognostic factor for both DFS and OS in stage II/III NSCLC [15]. The authors of the Ricciuti et al. study found a correlation between complete loss of ATM expression in tumors and a higher likelihood of smoking history [8]. However, our study did not discover a similar association. Patients with low ATM expression exhibited worse survival compared to those with high ATM expression. The effect of ATM expression on survival was more evident in advanced-stage (II/III) NSCLC patients [15]. In our study, patients with low ATM expression had significantly longer PFS compared to those with high expression. In Vokes et al.s' study, ATM mutations were associated with improved survival in patients treated with chemoimmunotherapy [9]. The Ricciuti et al. study did not find a statistically significant difference in treatment outcomes (ORR, PFS, and OS) based on ATM mutation status in patients receiving PD-(L)1 immune checkpoint blockade with platinum doublet chemotherapy, primarily in the first-line setting [8]. However, there was a numerical trend towards a higher ORR in the ATM mutant group compared to the ATM wild-type group [8]. Our study, using logistic regression analysis, found that ATM expression is a significant predictor of treatment response in patients with metastatic NSCLC receiving pembrolizumab-based therapy. Patients with high ATM expression had a significantly lower likelihood of responding to treatment (OR: 0.06, p=0.006, 95% CI: 0.08-0.48). Our findings were thus compatible with the literature [8].

Our findings suggest that ATM expression is a clinically relevant biomarker in NSCLC. Assessing ATM expression could aid in identifying patients who may benefit from alternative treatment approaches or targeted therapies. Additional studies are required to validate these results and explore the underlying biological mechanisms linking ATM expression to patient outcomes. Given the limitations of current biomarkers like PD-L1 and TMB, and the increasing number of treatment options, additional biomarkers are necessary to guide clinical decisions effectively. These biomarkers may also be important in early-stage treatments like neoadjuvant and adjuvant therapy [16–18].

This study has several limitations, including its retrospective design and relatively small sample size. Additionally, the generalizability of our findings may be limited to patients treated with pembrolizumab-based therapy. However, we believe that our study will contribute to the literature because it only included patients who received pembrolizumab or pembrolizumab and chemotherapy as first-line treatment and showed that ATM expression in this population is both a prognostic factor for survival and a predictive factor for treatment.

5. Conclusions

In conclusion, our study suggests that ATM expression is a valuable biomarker for predicting patient outcomes in metastatic NSCLC treated with pembrolizumab-based treatment in the first-line setting. Further research is necessary to confirm these findings and explore the potential clinical applications of targeting ATM in this patient population. Future studies should aim to validate our findings in larger, prospective cohorts and investigate the underlying mechanisms through which ATM expression affects patient outcomes. Additionally, exploring the potential therapeutic benefits of targeting ATM in NSCLC patients with high ATM expression is warranted.

Author Contributions: J.H: Conceptualization, Methodology, Writing – original draft. H.M: Data curation. A.B: Supervision, Conceptualization, Methodology. E.K: Software, Validation, Data curation. O.A: Data curation. O.F.O, O.Y and O.O: Data curation, Visualization, Investigation. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Local Ethics Committee at the Medipol University *(Istanbul, Turkey)*, on March 18, 2024 (decision number: 10840098-202.3.02-2000), and we confirm that all methods were performed in accordance with the relevant guidelines and regulation.

Informed Consent Statement: Written informed consent was obtained from all participating patients, or their designated relatives.

Data Availability Statement: The data supporting this study's findings are not openly available. Further enquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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