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The Impact of KRAS Mutation on Treatment Response and Survival in Patients with Metastatic Lung Adenocarcinoma Receiving First-line Systemic Therapy

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ABSTRACT

Objective: The prognostic and predictive significance of kirsten rat sarcoma viral oncogene homologue (KRAS) mutations in metastatic non-small cell lung cancer remains controversial, particularly in the immunotherapy era. Most previous studies compared KRAS-mutant tumors with heterogeneous KRAS wild-type populations that included other oncogenic driver alterations. This study aimed to evaluate the clinical impact of isolated KRAS mutations in patients with metastatic lung adenocarcinoma receiving first-line systemic therapy.

Material and Methods: This retrospective single-center study included patients with metastatic lung adenocarcinoma who underwent next-generation sequencing (NGS) between January 2023 and December 2025. Patients were categorized into two groups: those with isolated KRAS-mutant tumors and those with pan-wild tumors without any detectable oncogenic alterations on NGS. Patients with co-occurring oncogenic alterations were excluded. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and Cox regression analysis.

Results: A total of 75 patients were included, comprising 28 with isolated KRAS mutations and 47 without detectable oncogenic alterations. Programmed death-ligand 1 expression ≥50% was significantly more frequent in the KRAS-mutant group (p=0.001). However, KRAS mutation status was not significantly associated with PFS or OS in either univariate or multivariate analyses. Median PFS was 10.77 months in the KRAS-mutant group and 7.84 months in the pan-wild group (p=0.597), while median OS was 18.97 months in the KRAS-mutant group and 18.27 months in the pan-wild group (p=0.926). Similarly, no significant differences in survival were observed between the immunotherapy-containing and chemotherapy-alone subgroups.

Conclusion: Isolated KRAS mutations were not associated with significantly different survival outcomes compared with tumors lacking detectable oncogenic alterations. These findings suggest that KRAS mutation status alone may have limited prognostic value in metastatic lung adenocarcinoma.

Keywords: Immunotherapy; KRAS mutation; metastatic lung adenocarcinoma; survival outcomes

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, accounting for a substantial proportion of cancer deaths despite advances in diagnosis and treatment.[1] Non-small cell lung cancer (NSCLC) constitutes approximately 80-85% of all lung cancer cases, with adenocarcinoma being the most common histological subtype.[2] A significant proportion of patients are diagnosed at an advanced or metastatic stage, where curative treatment options are limited and the prognosis remains poor. In patients with stage IV disease, the 5 years overall survival (OS) rate is generally below 10%, underscoring its aggressive nature.[3,4]

In recent years, the management of metastatic NSCLC has been transformed by the integration of molecular profiling and the development of targeted therapies and immune

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checkpoint inhibitors. While patients with actionable driver alterations, such as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) and ROS1 rearrangements, benefit significantly from targeted therapies, a substantial proportion lack these alterations. For these patients, platinum-based chemotherapy, alone or combined with immunotherapy, remains the cornerstone of first-line treatment. However, treatment responses remain heterogeneous, highlighting the need for reliable biomarkers to better predict therapeutic efficacy and survival outcomes.[5]

Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations represent the most common oncogenic driver alterations in NSCLC, particularly in lung adenocarcinoma, where they are detected in approximately 20-40% of cases.[6,7] These mutations are strongly associated with tobacco exposure and predominantly occur at codons 12 and 13, with G12C, G12V, and G12D being the most frequent subtypes.[8] KRAS encodes a small GTPase that plays a central role in regulating key intracellular signaling pathways involved in cell proliferation, differentiation, and survival. Activating mutations in KRAS lead to constitutive pathway activation, resulting in uncontrolled tumor growth and disease progression.[9]

Despite its high prevalence, the prognostic and predictive role of KRAS mutations in metastatic NSCLC remains controversial. In the era of cytotoxic chemotherapy, several studies suggested that KRAS mutations were associated with poorer survival outcomes and reduced response to platinum-based regimens.[10,11] However, since the introduction of immune checkpoint inhibitors, emerging evidence indicates that KRAS-mutant tumors may exhibit enhanced sensitivity to immunotherapy, potentially due to a higher tumor mutational burden and increased immunogenicity.[12,13] Nevertheless, real-world studies and retrospective analyses have reported inconsistent findings, with some demonstrating improved outcomes in KRAS-mutant patients receiving immunotherapy, while others have shown no significant difference or even worse survival compared to KRAS wild-type patients.[14-16]

Moreover, most of the existing studies have compared KRAS-mutant tumors with heterogeneous KRAS wild-type groups that may include other oncogenic driver alterations, potentially confounding the interpretation of results.[14] Therefore, the independent clinical impact of KRAS mutations, particularly in the absence of other detectable driver alterations, remains unclear. In this context, the present study aimed to evaluate whether the presence of an isolated KRAS mutation influences treatment response and survival outcomes in patients with metastatic lung adenocarcinoma receiving first-line systemic therapy.

MATERIAL AND METHODS

This study was a retrospective, single-center, observational analysis conducted at a tertiary referral center. Patients diagnosed with metastatic lung adenocarcinoma between January 2023 and December 2025 were screened for eligibility. Only patients who underwent next-generation sequencing (NGS) as part of routine clinical practice were included.

Targeted DNA- and RNA-based NGS was performed using the Archer VariantPlex Expanded panel (Invitae, Boulder, CO, USA). The panel routinely assessed clinically relevant genomic alterations in NSCLC, including *EGFR, BRAF, KRAS, ERBB2, PIK3CA, STK11, KEAP1, TP53, ALK, NTRK1, NTRK2, NTRK3, RET, ROS1, NRG1, MET, FGFR1, FGFR2, FGFR3*, and *NF1*. The molecular findings were used to classify patients as having isolated KRAS-mutant tumors or pan-wild tumors without detectable oncogenic driver alterations.

Eligible patients were required to have histologically confirmed stage IV lung adenocarcinoma and to have received first-line systemic therapy consisting of platinum-based chemotherapy alone or combined with immune checkpoint inhibitors. To ensure adequate evaluation of treatment response, only patients who received at least four cycles of first-line therapy and had a radiological response assessment were included in the analysis.

Patients were categorized into two groups according to their molecular status: those harboring isolated KRAS mutations (KRAS-mutant group) and those without any detectable oncogenic alterations by NGS (pan-wild group). To minimize potential confounding effects, patients with co-occurring oncogenic driver alterations, including EGFR mutations, ALK and ROS1 rearrangements, BRAF mutations, and other actionable genomic alterations, were excluded. A total of 75 patients were included in the final analysis, of whom 28 were in the KRAS-mutant group and 47 were in the pan-wild group.

Clinical and pathological data, including age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, sites of metastasis, and treatment regimens, were collected retrospectively from electronic medical records. Treatment response was evaluated radiologically according to the Response Evaluation Criteria in Solid Tumors version 1.1.

Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to identify factors associated with OS and PFS. Variables with a p value <0.20 in univariate analysis, along with clinically relevant factors, were included in the multivariate model. Hazard ratios with 95% confidence intervals (CIs) were calculated.

A two-sided p-value <0.05 was considered statistically significant.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (range), while categorical variables were summarized as frequencies and percentages. Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate.

OS was defined as the time from initiation of first-line therapy to death from any cause or to last follow-up. Progression-free survival (PFS) was defined as the time from initiation of first-line therapy to disease progression or death, whichever occurred first. Follow-up duration was calculated from initiation of first-line systemic therapy to the date of death or last clinical follow-up. The median follow-up duration was calculated from the individual follow-up times. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

This retrospective study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: 174, date: 16.04.2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived by the same Ethics Committee because the study was retrospective.

RESULTS

A total of 75 patients with metastatic lung adenocarcinoma who met the inclusion criteria were included in the study. Among these, 28 patients (37.3%) had tumors harboring isolated KRAS mutations, while 47 patients (62.7%) had no detectable oncogenic alterations by NGS (pan-wild group). The median follow-up time was 17.03 months, and the mean age of the study population was 63.33±8.69 years. The baseline demographic and clinical characteristics of the study population are summarized in Table 1.

Among the 28 patients with KRAS-mutant tumors, KRAS G12C was the most common subtype, accounting for 13 cases (46.4%). The remaining KRAS mutation subtypes included G12V (n=4; 14.3%), G12D (n=4; 14.3%), G12A (n=2; 7.1%), G12S (n=1; 3.6%), G12R (n=1; 3.6%), G13D (n=1; 3.6%), Q61H (n=1; 3.6%), and Q61L (n=1; 3.6%). Overall, 15 patients (53.6%) harbored non-G12C KRAS variants.

The majority of patients in both groups were male, and the sex distribution was comparable between groups. Similarly, smoking status, ECOG performance status, comorbidity, and stage at diagnosis were balanced, with no statistically significant differences observed.

However, a significant difference was noted in programmed death-ligand 1 (PD-L1) expression levels between the groups (p=0.001), with a higher proportion of patients with PD-L1 ≥50% in the KRAS-mutant group. In addition, distant lymph node metastases were significantly more frequent in the pan-wild group (p=0.018). No significant differences were observed between groups regarding other metastatic sites, including brain, liver, bone, adrenal, and contralateral lung. Likewise, the distribution of first-line treatment regimens and the best overall response rates were similar between the two groups.

Univariate and multivariate Cox regression analyses were performed to identify factors associated with PFS (Table 2). In univariate analysis, treatment with chemotherapy plus immunotherapy was significantly associated with improved PFS compared to chemotherapy alone (p<0.001). In contrast, KRAS mutation status was not significantly associated with PFS (p=0.597). Similarly, none of the other evaluated variables, including ECOG performance status, PD-L1 expression, and metastatic sites, showed a significant association with PFS.

In multivariate analysis, treatment with chemotherapy plus immunotherapy remained an independent predictor of improved PFS compared to chemotherapy alone (p<0.001). In contrast, KRAS mutation status was not independently associated with PFS (p=0.264). Likewise, ECOG performance status and PD-L1 expression did not demonstrate a statistically significant association with PFS in the multivariate model.

Univariate and multivariate Cox regression analyses were performed to identify factors associated with OS (Table 3). In univariate analysis, treatment with chemotherapy plus immunotherapy was significantly associated with improved OS compared with chemotherapy alone (p=0.017). In contrast, KRAS mutation status was not significantly associated with OS (p=0.926). None of the other evaluated variables demonstrated a statistically significant association with OS in the univariate analysis.

In multivariate analysis, treatment with chemotherapy plus immunotherapy remained an independent predictor of improved OS (p=0.003). ECOG performance status was also identified as an independent prognostic factor, with worse performance status associated with shorter OS (p=0.020). In addition, the absence of bone metastasis was independently associated with improved OS (p=0.030). KRAS mutation status

TABLE 1: Baseline demographic and clinical characteristics of patients with metastatic lung adenocarcinoma according to KRAS mutation status.

		KRAS-mutant (n=28)	Pan-wild (n=47)	Total (n=75)	p-value
Sex	Female	5 (17.9%)	8 (17.0%)	13 (17.3%)	0.926
	Male	23 (82.1%)	39 (83.0%)	62 (82.7%)	
Smoking status	Yes	25 (89.3%)	45 (95.7%)	70 (93.3%)	0.278
	No	3 (10.7%)	2 (4.3%)	5 (6.7%)	
ECOG-PS	0	17 (60.7%)	28 (59.6%)	45 (60.0%)	0.922
	1	11 (39.3%)	19 (40.4%)	30 (40.0%)	
Comorbidity	Yes	23 (82.1%)	31 (66.0%)	54 (72.0%)	0.131
	No	5 (17.9%)	16 (34.0%)	21 (28.0%)	
Stage at diagnosis	I-III	5 (17.9%)	7 (14.9%)	12 (16.0%)	0.400
	IV	23 (82.1%)	40 (85.1%)	63 (84.0%)	
PD-L1 expression	0%	5 (17.9%)	24 (51.1%)	29 (38.7%)	**0.001**
	1-49%	12 (42.9%)	20 (42.6%)	32 (42.7%)	
	≥50%	11 (39.3%)	3 (6.4%)	14 (18.7%)	
Contralateral lung metastasis	Yes	15 (53.6%)	20 (42.6%)	35 (46.7%)	0.355
	No	13 (46.4%)	27 (57.4%)	40 (53.3%)	
Brain metastasis	Yes	6 (21.4%)	15 (31.9%)	21 (28.0%)	0.328
	No	22 (78.6%)	32 (68.1%)	54 (72.0%)	
Liver metastasis	Yes	1 (3.6%)	6 (12.8%)	7 (9.3%)	0.186
	No	27 (96.4%)	41 (87.2%)	68 (90.7%)	
Bone metastasis	Yes	17 (60.7%)	32 (68.1%)	49 (65.3%)	0.516
	No	11 (39.3%)	15 (31.9%)	26 (34.7%)	
Adrenal metastasis	Yes	3 (10.7%)	14 (29.8%)	17 (22.7%)	0.056
	No	25 (89.3%)	33 (70.2%)	58 (77.3%)	
Distant lymph node metastasis	Yes	14 (50.0%)	36 (76.6%)	50 (66.7%)	**0.018**
	No	14 (50.0%)	11 (23.4%)	25 (33.3%)	
First-line treatment	Chemotherapy	14 (50.0%)	32 (68.1%)	46 (61.3%)	0.298
	Chemo + IO	13 (46.4%)	14 (29.8%)	27 (36.0%)	
	IO	1 (3.6%)	1 (2.1%)	2 (2.7%)	
Best response	PR	19 (67.9%)	31 (66.0%)	50 (66.7%)	0.700
	SD	1 (3.6%)	4 (8.5%)	5 (6.7%)	
	PD	8 (28.6%)	12 (25.5%)	20 (26.7%)	
Progression	Yes	18 (64.3%)	28 (59.6%)	46 (61.3%)	0.685
	No	10 (35.7%)	19 (40.4%)	29 (38.7%)	

ECOG-PS: Eastern Cooperative Oncology Group performance status; KRAS: Kirsten rat sarcoma viral oncogene homologue; PD-L1: programmed death-ligand 1; IO: immunotherapy; PR: partial response; SD: stable disease; PD: progressive disease.

was not significantly associated with OS in the multivariate model (p=0.085).

Kaplan-Meier survival analyses were performed to compare PFS and OS between patients with isolated KRAS mutations and those without detectable oncogenic alterations (Figure 1).

The median PFS was 10.77 months (95% CI: 7.18-14.35) in the KRAS-mutant group and 7.84 months (95% CI: 6.12-9.55) in the pan-wild group, with no statistically significant difference observed between the groups (p=0.597) (Figure 1A).

Similarly, the median OS was 18.97 months (95% CI: 11.56-26.37) in the KRAS-mutant group and 18.27 months (95% CI: 15.02-21.52) in the pan-wild group, with no significant difference between the groups (p=0.926) (Figure 1B).

TABLE 2: Univariate and multivariate Cox regression analysis of factors associated with PFS.				
Variable	**Univariate HR (95% CI)**	**p-value**	**Multivariate HR (95% CI)**	**p-value**
Sex				
Female	Reference			
Male	0.74 (0.37-1.47)	0.401		
Age				
≥65 years	Reference			
<65 years	1.14 (0.60-2.16)	0.683		
ECOG-PS				
0	Reference		Reference	
1	1.29 (0.67-2.45)	0.446	1.83 (0.93-3.61)	0.081
Comorbidity				
No	Reference			
Yes	0.75 (0.38-1.47)	0.400		
KRAS status				
Pan-wild	Reference		Reference	
Mutant	1.18 (0.64-2.17)	0.597	0.66 (0.32-1.36)	0.264
PD-L1				
0	Reference		Reference	
1-49	0.59 (0.31-1.14)	0.117	0.58 (0.29-1.16)	0.124
≥50	0.68 (0.29-1.57)	0.370	0.66 (0.24-1.80)	0.415
Contralateral lung metastasis				
No	Reference			
Yes	1.04 (0.57-1.88)	0.898		
Brain metastasis				
No	Reference			
Yes	0.93 (0.48-1.78)	0.825		
Liver metastasis				
No	Reference			
Yes	1.17 (0.49-2.80)	0.728		
Bone metastasis				
No	Reference			
Yes	0.81 (0.45-1.48)	0.501		
Adrenal metastasis				
No	Reference			
Yes	1.03 (0.49-2.16)	0.927		
Distant lymph node metastasis				
No	Reference			
Yes	1.54 (0.79-3.03)	0.207		
Treatment group				
Chemotherapy	Reference		Reference	
Chemo + IO	0.23 (0.10-0.53)	**<0.001**	0.20 (0.08-0.48)	**<0.001**
IO	1.37 (0.18-10.24)	0.760	1.35 (0.15-11.83)	0.788

CI: Confidence interval; HR: Hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; ECOG-PS: Eastern Cooperative Oncology Group performance status; IO: Immunotherapy; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; OS: Overall survival.

TABLE 3: Univariate and multivariate Cox regression analysis of factors associated with OS.				
Variable	**Univariate HR (95% CI)**	**p-value**	**Multivariate HR (95% CI)**	**p-value**
Sex				
Female	Reference			
Male	0.69 (0.31-1.52)	0.357		
Age				
≥65 years	Reference			
<65 years	1.51 (0.75-3.04)	0.250		
ECOG-PS				
0	Reference		Reference	
1	1.67 (0.83-3.34)	0.148	2.40 (1.15-5.01)	**0.020**
Comorbidity				
No	Reference			
Yes	1.02 (0.47-2.20)	0.964		
KRAS status				
Pan-wild	Reference		Reference	
Mutant	0.97 (0.48-1.95)	0.926	0.47 (0.20-1.11)	0.085
PD-L1				
0	Reference		Reference	
1-49	0.82 (0.39-1.74)	0.608	0.73 (0.33-1.64)	0.453
≥50	0.63 (0.22-1.84)	0.401	0.61 (0.17-2.19)	0.452
Contralateral lung metastasis				
No	Reference			
Yes	1.19 (0.60-2.33)	0.621		
Brain metastasis				
No	Reference			
Yes	0.72 (0.32-1.62)	0.429		
Liver metastasis				
No	Reference			
Yes	0.81 (0.29-2.23)	0.687		
Bone metastasis				
No	Reference			
Yes	1.84 (0.87-3.90)	0.110	2.40 (1.08-5.31)	**0.030**
Adrenal metastasis				
No	Reference			
Yes	1.22 (0.55-2.72)	0.623		
Distant lymph node metastasis				
No	Reference			
Yes	1.58 (0.73-3.42)	0.247		
Treatment group				
Chemotherapy	Reference		Reference	
Chemo + IO	0.23 (0.07-0.77)	**0.017**	0.14 (0.04-0.52)	**0.003**
IO	0.40 (0.05-3.17)	0.385	0.21 (0.02-2.55)	0.223

CI: Confidence interval; HR: Hazard ratio; KRAS: Kirsten rat sarcoma viral oncogene homologue; ECOG-PS: Eastern Cooperative Oncology Group performance status; IO: Immunotherapy; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; OS: Overall survival.

A subgroup analysis was performed in patients who received immunotherapy-containing regimens (n=14 in the KRAS-mutant group and n=15 in the pan-wild group). In this subgroup, the median PFS was 14.07 months (95% CI: 13.17-14.96) in the KRAS-mutant group and 13.53 months (95% CI: 2.52-24.55) in the pan-wild group, with no statistically significant difference between the groups (p=0.633) (Figure 2). OS data in this subgroup were immature at the time of analysis and were therefore not reported.

A separate subgroup analysis was performed among patients who received chemotherapy alone (n=14 in the KRAS-mutant group and n=32 in the pan-wild group). In this subgroup, the median PFS was 4.97 months (95% CI: 0-11.32) in the KRAS-mutant group and 7.23 months (95% CI: 6.14-8.32) in the pan-wild group, with no statistically significant difference between the groups (p=0.709). These findings were consistent with those observed in the overall cohort.

At the time of analysis, 13 patients (46.4%) in the KRAS-mutant group had died and 15 patients (53.6%) were alive, whereas 21 patients (44.7%) in the pan-wild group had died and 26 patients (55.3%) were alive.

DISCUSSION

In the present study, we evaluated the impact of isolated KRAS mutations on treatment response and survival outcomes in patients with metastatic lung adenocarcinoma receiving first-line systemic therapy. Our findings demonstrated that KRAS mutation status was not significantly associated with PFS or OS in either univariate or multivariate analyses. Similarly, Kaplan-Meier analyses showed no statistically significant differences in survival outcomes between the KRAS-mutant and pan-wild groups. In contrast, the use of chemoimmunotherapy was independently associated with improved PFS and OS compared with chemotherapy alone. Notably, although patients with KRAS-mutant tumors had significantly higher PD-L1 expression levels, this did not translate into superior survival outcomes.

Previous studies investigating the prognostic role of KRAS mutations in metastatic NSCLC have reported conflicting results. In the pre-immunotherapy era, several studies suggested that KRAS mutations were associated with poorer clinical outcomes and reduced sensitivity to platinum-based chemotherapy. Marabese et al.[10] demonstrated that KRAS-mutant NSCLC patients receiving first-line platinum-containing chemotherapy had significantly shorter survival outcomes compared with KRAS wild-type patients. Similarly, Eklund et al.[11] reported that KRAS mutations were associated with inferior survival in metastatic NSCLC, supporting the hypothesis that KRAS-driven tumors may exhibit more aggressive biological behavior. However, more recent studies conducted in the immunotherapy era have produced inconsistent findings regarding the prognostic and predictive value of KRAS mutations.[14]

In our study, KRAS mutation status was not independently associated with either PFS or OS. These findings are in line with several contemporary real-world analyses demonstrating that KRAS mutations alone may not confer a distinct survival disadvantage in patients receiving modern systemic therapies.[17,18] Importantly, unlike many previous reports, our study excluded patients harboring other actionable oncogenic alterations and compared KRAS-mutant tumors with a pan-wild population lacking detectable driver mutations on NGS. This more homogeneous comparator group may have reduced potential molecular confounding and allowed a more accurate assessment of the independent clinical impact of KRAS mutations.

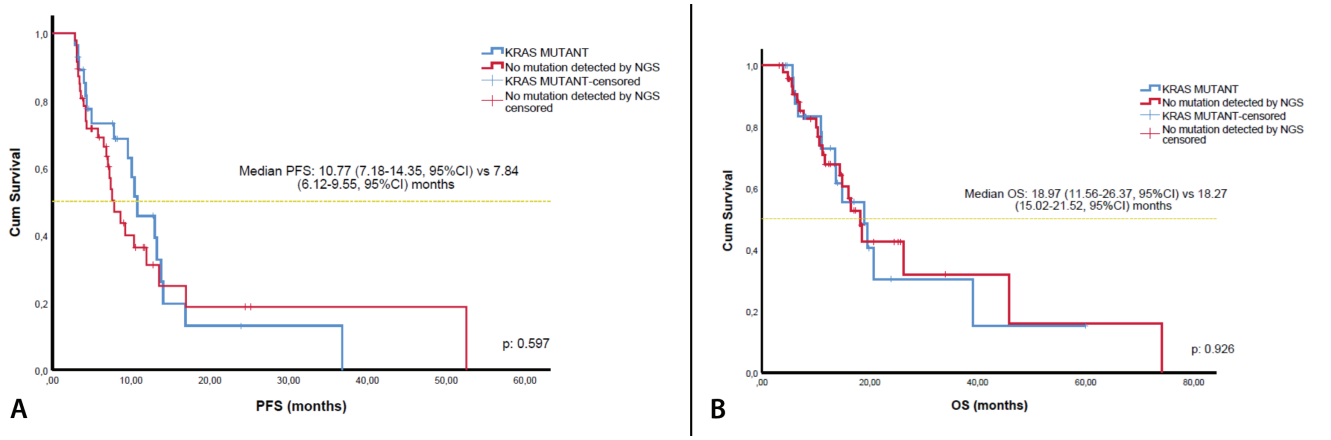

FIGURE 1: Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) according to KRAS mutation status in the overall study population (n=75; KRAS-mutant, n=28; pan-wild, n=47). **(A)** PFS; **(B)** OS.

KRAS: Kirsten rat sarcoma viral oncogene homologue

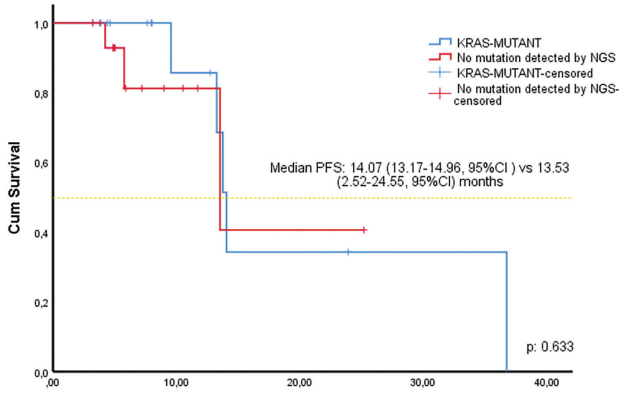

FIGURE 2: Kaplan-Meier curve for progression-free survival (PFS) according to KRAS mutation status in patients receiving immunotherapy-containing regimens (n=29; KRAS-mutant, n=14; pan-wild, n=15).

NGS: Next-generation sequencing; CI: Confidence interval; KRAS: Kirsten rat sarcoma viral oncogene homologue

Notably, patients with KRAS-mutant tumors in our cohort exhibited significantly higher PD-L1 expression levels compared with the pan-wild group. This finding is consistent with previous studies reporting an association between KRAS mutations and increased tumor immunogenicity.[19] KRAS-mutant NSCLC has been associated with smoking-related mutational signatures, higher tumor mutational burden, and a more inflamed tumor microenvironment, all of which may contribute to increased PD-L1 expression and enhanced immune recognition.[20] In particular, several studies have demonstrated that PD-L1 ≥50% is more frequently observed in KRAS-mutant tumors than in KRAS wild-type populations.[21] Despite this biological association, the higher PD-L1 expression observed in our KRAS-mutant cohort did not translate into superior survival outcomes, suggesting that PD-L1 expression alone may be insufficient to predict prognosis in this molecular subgroup.

In addition to KRAS mutation status, accumulating evidence suggests that co-occurring genomic alterations may substantially influence the biological behavior of KRAS-mutant NSCLC. In particular, concurrent STK11 and KEAP1 mutations have consistently been associated with an immunosuppressive tumor microenvironment, reduced responsiveness to immune checkpoint inhibitors, and poorer survival outcomes, whereas TP53 co-mutations have been linked to increased tumor immunogenicity and may be associated with improved responses to immunotherapy.[22-24] Unfortunately, information regarding co-mutation status was not routinely available in our cohort; therefore, the potential impact of these alterations could not be evaluated. Future studies incorporating comprehensive genomic profiling are warranted to better define the prognostic and predictive significance of these co-mutations in patients with KRAS-mutant NSCLC.

In the subgroup analysis of patients receiving immunotherapy-containing regimens, no statistically significant difference in PFS was observed between the KRAS-mutant and pan-wild groups. Several previous studies have suggested that KRAS-mutant NSCLC may derive greater benefit from immune checkpoint inhibitors compared with KRAS wild-type tumors, potentially due to higher PD-L1 expression, smoking-related mutational signatures, and increased tumor immunogenicity.[19,25] However, despite these findings, other studies have reported neutral survival outcomes between KRAS-mutant and KRAS wild-type populations in the immunotherapy era.[18,26] Differences in study populations, co-occurring genomic alterations, KRAS mutation subtypes, and treatment strategies may partly explain these heterogeneous findings across studies. In our cohort, the exclusion of patients with other concomitant oncogenic alterations may have contributed to the relatively comparable outcomes observed between the two groups.

A separate subgroup analysis among patients treated with chemotherapy alone also demonstrated no significant difference in PFS between the KRAS-mutant and pan-wild groups. In the pre-immunotherapy era, KRAS mutations were frequently considered a negative prognostic factor and were associated with reduced sensitivity to platinum-based chemotherapy in several studies.[10,27] However, our findings suggest that isolated KRAS mutations alone may not substantially influence treatment outcomes in patients receiving conventional chemotherapy. These results further support the notion that the clinical impact of KRAS mutations may be strongly influenced by accompanying molecular alterations and tumor biological heterogeneity rather than by KRAS status alone.

Study Limitations

This study has several strengths. First, unlike many previous studies, patients with other concomitant oncogenic alterations were excluded, allowing a more homogeneous comparison between KRAS-mutant and pan-wild populations. Second, all patients underwent NGS, enabling more accurate molecular characterization of the study cohort. In addition, both OS and PFS were evaluated in the overall cohort as well as in treatment-specific subgroups, providing a more comprehensive assessment of the clinical impact of KRAS mutations in metastatic lung adenocarcinoma.

Several limitations of this study should be acknowledged. First, the retrospective and single-center design may have introduced potential selection bias. Second, the relatively small sample size, particularly in subgroup analyses, may have

limited the statistical power to detect modest differences in survival outcomes between groups. Therefore, the absence of statistically significant differences should be interpreted with appropriate caution. In addition, KRAS mutation subtypes and co-mutation profiles were not analyzed separately, which may have influenced treatment response and survival outcomes. KRAS G12C, which was the most common KRAS subtype in our cohort, was also not evaluated separately despite the ongoing development of first-line treatment strategies combining KRAS G12C inhibitors with immunotherapy or chemotherapy. Finally, the relatively short follow-up duration and immature OS data in some subgroups may limit the interpretation of long-term outcomes.

Overall, isolated KRAS mutations were not significantly associated with PFS or OS when compared with patients without detectable oncogenic alterations in metastatic lung adenocarcinoma receiving first-line systemic therapy. Although KRAS-mutant tumors exhibited higher PD-L1 expression, this did not translate into superior survival outcomes. These findings suggest that KRAS mutation status alone may have limited prognostic value in the absence of other concomitant oncogenic alterations.

CONCLUSION

In this retrospective single-center study, isolated KRAS mutations did not appear to significantly influence survival outcomes in patients with metastatic lung adenocarcinoma receiving first-line systemic therapy. No significant differences in survival outcomes were observed between the KRAS-mutant and pan-wild groups in either the immunotherapy-containing regimen subgroup or the chemotherapy-alone subgroup. Further prospective studies with larger patient populations and comprehensive molecular analyses are needed to better clarify the clinical significance of KRAS mutations in metastatic NSCLC.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital (approval number: 174, date: 16.04.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.A., Ş.D.S., A.E.Ö., Concept: O.A., M.E., K.E., Design: O.A., K.E., Data Collection or Processing: O.A., Ş.D.S., A.E.Ö., Analysis or Interpretation: O.A., F.A., Z.S.İ., Literature Search: O.A., M.E., F.A., Writing: O.A., Z.S.İ.

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