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ORIGINAL RESEARCH ARTICLE

Deciphering the co-mutation landscape and clinical implications in *SMARCA4*-mutant lung adenocarcinoma

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Abstract

Introduction: Lung adenocarcinoma (LUAD) exhibits significant genomic heterogeneity, with *SMARCA4* mutations often co-occurring with other mutated genes that may shape disease progression and patient outcomes.

Objective: The objective of the study is to investigate the impact of co-mutated genes on the prognosis and immunotherapeutic response in *SMARCA4*-mutant LUAD.

Methods: Genomic and clinical data from *SMARCA4*-mutant LUAD patients were extracted from the Memorial Sloan Kettering cohort through cBioPortal, with overall survival (OS) as the primary endpoint. We systematically assessed the most frequent coexisting genomic alterations.

Results: Within a cohort of 5,957 LUAD patients, we identified 8% (n = 477) harboring *SMARCA4* mutations. The most frequent co-mutations included *TP53* (49%), *STK11* (48%), *KEAP1* (46%), *KRAS* (39%), and *CDKN2A* (33%). *TP53* co-mutations exhibited significant mutual exclusivity with *STK11*, *KEAP1*, *KRAS*, and *CDKN2A*. Multivariable analysis revealed that *KRAS*, *STK11*, and *KEAP1* co-mutations independently predicted shortened survival, whereas *CDKN2A* and *TP53* co-mutation status showed no significant prognostic impact. Notably, *TP53* co-mutations were associated with elevated tumor mutational burden and higher programmed death-ligand 1 expression. In Stage IV *SMARCA4*-mutant LUAD patients, an improved prognosis associated with co-mutation of *TP53* and *KRAS* was observed with immune checkpoint inhibitor therapy.

Conclusion: In *SMARCA4*-mutant LUAD patients, *TP53*, *STK11*, *KEAP1*, *KRAS*, and *CDKN2A* were the most frequent co-occurring genomic alterations. Multivariable analysis identified *KRAS*, *STK11*, and *KEAP1* co-mutations as independent adverse prognostic factors. Notably, tumors harboring *STK11*/*KEAP1* double mutations or *KRAS*/*STK11*/*KEAP1* triple mutations exhibited extremely poor OS, whereas *TP53* co-mutations correlated with favorable outcomes and significant immunotherapy benefit. Intriguingly, *TP53* mutations demonstrated mutual exclusivity with *KRAS*, *STK11*, and *KEAP1* alterations, suggesting divergent oncogenic trajectories.

Keywords: *SMARCA4*; Lung adenocarcinoma; Co-mutation; Immunotherapy; Prognosis; Exclusivity

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1. Introduction

Lung cancer is the most common malignancy worldwide and one of the leading causes of cancer-related deaths globally.[1] It is classified into two main categories: non-small cell lung cancer (NSCLC) and small cell lung cancer, with lung adenocarcinoma (LUAD) being the most prevalent subtype of NSCLC. However, traditional histological classification is unable to meet the demands for precision treatment of LUAD. The advent of next-generation sequencing (NGS) has revealed a series of oncogenic alterations, creating opportunities for targeted therapies.[2] At present, molecular testing for advanced LUAD routinely includes mutations in *EGFR*, *BRAF* V600E, *KRAS* G12C, *MET* exon 14, *ALK*, *ROS1*, *NTRK*, and *RET*. Corresponding targeted therapies have been progressively approved,[3,4] making molecular subtyping increasingly crucial in cancer diagnosis and treatment. Understanding genomic alterations not only guides the management of individual cancers but also reveals potential mechanisms of resistance to targeted therapies and immunotherapies.[5,6]

With advances in molecular biology, an increasing number of genetic mutations have been identified as closely associated with the initiation and progression of LUAD, among which *SMARCA4* gene mutations have garnered significant attention. *SMARCA4* mutations account for approximately 8–10% of lung cancer cases.[7] *SMARCA4*, a core component of the SWI/SNF chromatin remodeling complex, plays a critical role in regulating gene expression, cell cycle control, and development across multiple tissues and organs.[8-11] Mutations in *SMARCA4* typically lead to loss-of-function in this complex, potentially causing chromatin structural abnormalities that influence tumorigenesis, progression, and prognosis. However, *SMARCA4*-mutant LUAD still lacks effective targeted therapeutic options comparable to those for *EGFR* or *ALK* alterations, limiting the applicability of traditional small-molecule targeted drugs. Current treatment strategies primarily rely on chemotherapy and immunotherapy.

Co-mutation refers to the concurrent presence of multiple genetic alterations within the same tumor. These mutations may interact synergistically, influencing tumorigenesis, progression, therapeutic response, and prognosis. Different mutational combinations may drive distinct biological mechanisms, and tumor cell models with varying molecular backgrounds could yield conflicting conclusions.[12,13] Consequently, co-mutation analysis provides systematic association studies of genomic alterations to identify clinically relevant variants that may affect prognosis and guide therapeutic decision-making.

Studies have revealed that *SMARCA4* mutations frequently co-occur with other driver gene alterations such as *TP53*, *KRAS*, and *KEAP1*.[7,14] In *SMARCA4*-mutant LUAD patients, this complex mutational network not only affects cellular proliferation and survival but may also correlate closely with tumor microenvironment remodeling and features like elevated tumor mutational burden (TMB). However, *SMARCA4*-mutant LUAD demonstrates molecular heterogeneity and is associated with divergent clinical outcomes and variable responses to immunotherapy. For instance, *SMARCA4*-mutant LUAD patients often exhibit high TMB, which might predict favorable responses to immunotherapy. Some studies have reported improved clinical outcomes in *SMARCA4*-mutant patients treated with immune checkpoint inhibitors.[15,16] Conversely, other studies suggest that the prognosis of this population is not associated with immunotherapy.[17-19] Therefore, in-depth exploration of co-mutation patterns in *SMARCA4*-mutant LUAD and their impact on patient prognosis holds significant clinical implications for developing personalized treatment strategies.

Furthermore, dedicated molecular subtyping studies focusing on *SMARCA4*-mutant LUAD remain scarce. This study aims to comprehensively characterize the impact of co-mutations on the clinical outcome and immune efficacy of *SMARCA4*-altered LUAD. Leveraging a retrospective cohort of 401 patients from the Memorial Sloan Kettering Cancer Center-Clinicogenomic Harmonized Oncology Real-world Data (MSK-CHORD) database,[20] we dissected the complex mutational landscape of *SMARCA4*-mutant LUAD. Through stratified survival analyses, we explored prognostic disparities across distinct co-mutation clusters. In addition, we evaluated the efficacy of immune checkpoint inhibitor regimens in this highly aggressive LUAD subset, analyzing survival outcomes to identify potential therapeutic vulnerabilities.

2. Materials and methods

2.1. Materials

Genomic and clinical data for this study were obtained from the MSK-CHORD cohort, accessible through cBioPortal (https://www.cbioportal.org)—a publicly available repository for cancer research. MSK-CHORD dataset encompasses both summary visualizations and clinical information obtained from the targeted sequencing of 25,040 tumors sourced from 24,950 patients, including their matched normal samples, through the MSK-Integrated Mutation Profiling of Actionable Cancer Targets[21] platform. In addition, it incorporates clinical annotations, some of which were generated using natural language processing techniques. We extracted genomic

and clinicopathological data (including tumor stage at diagnosis, immunotherapy status, and clinical outcomes such as overall survival [OS]) from 401 LUAD samples (Table S1). Only one sample per patient was used in this study. We further assessed TMB and programmed death-ligand 1 (PD-L1) expression and selected a cohort of Stage IV LUAD patients who received immunotherapy for subsequent analysis.

2.2. Method

The "OncoPrint" module in cBioPortal enables visualization of the genomic alteration landscape (e.g., mutations, amplifications, deletions) of individual or multiple genes across tumor samples, along with the frequency of alterations. The "Comparison/Survival" module automatically generates Kaplan–Meier survival curves to compare OS between genomic alteration groups and wild-type counterparts. In addition, it employs the Wilcoxon test (for continuous variables, e.g., TMB) and Chi-square test (for categorical variables, e.g., PD-L1 positivity) to evaluate differences in TMB and PD-L1 expression across subgroups. The "Mutual Exclusivity" module demonstrates mutually exclusive or co-occurring relationships between genetic variants.

2.3. Statistical analysis

Prognostic analyses included 401 LUAD samples from the MSK-CHORD cohort. Univariable and multivariable Cox models evaluated clinical stage (Stage IV *vs*. Stage I-III) and co-mutations (*TP53*, *KRAS*, *STK11*, *KEAP1*, *CDKN2A*). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to identify independent predictors of survival. PD-L1 positivity rates were compared across subgroups using the χ^2 test or Fisher's exact test, as appropriate. Survival outcomes were analyzed through Kaplan–Meier curves with log-rank tests. All statistical tests were two-sided, and $p<0.05$ was considered significant. Analyses were performed in the Statistical Package for the Social Sciences software (version 29), and figures were generated using GraphPad Prism (version 9.5.1).

3. Results

3.1. The variation frequency and profiles of *SMARCA4* in LUAD

In the MSK-CHORD dataset, 5,957 LUAD patients underwent Integrated Mutation Profiling of Actionable Cancer Target sequencing, of whom 8% (n = 477) had a *SMARCA4* alteration, whereas the remaining 5,480 patients were identified as *SMARCA4* wild-type. *SMARCA4* variant types include in-frame mutations, missense mutations, splice mutations, truncating mutations, structural variants, amplifications, and deep deletions (Figure 1A). *SMARCA4* driver mutations were identified in 4% (n = 267) of cases; the mutation types included only missense mutations, splice mutations, truncating mutations, structural variants, and deep deletions (Figure 1B). We subsequently analyzed the frequency of *SMARCA4* alteration types, with missense and truncating mutations being the most common (Figure 1C). Variants of unknown significance predominantly occurred as missense mutations (Figure 1D). Notably, truncating mutations outnumbered missense mutations in cases with *SMARCA4* driver mutations (Figure 1E).

3.2. Distinct *SMARCA4* mutation types in LUAD

To investigate the clinical impact of *SMARCA4* alteration types, we first compared the prognosis of tumors with *SMARCA4* driver mutations (n = 267) and those with *SMARCA4* non-driver mutations (n = 210). Patients harboring driver mutations exhibited worse OS than those with non-driver mutations (median months overall: 13.08 vs. 26.99, HR: 1.387, 95% CI: 1.113–1.728, p=0.0039; Figure 2A). Next, we compared the genomic profiles of both groups. Among commonly mutated genes in lung cancer, the most frequent co-mutations in descending order were *TP53*, *STK11*, *KEAP1*, *KRAS*, and *CDKN2A*, with no statistically significant differences between the two groups (Figure 2B). Here, we sought to compare PD-L1 expression levels between the two groups. We found that patients with *SMARCA4* driver mutations exhibited a lower PD-L1 positivity rate (51.00% vs. 75.90%, p=0.0009; Figure 2C), which partially explains the poor prognosis observed in this subgroup. Furthermore, we compared the prognosis of tumors harboring *SMARCA4* missense mutations (n = 233) and those with *SMARCA4* non-missense mutations (n = 244). Patients with non-missense mutations exhibited worse OS than those with missense mutations (median months overall: 12.79 vs. 26.79, HR: 1.366, 95% CI: 1.097–1.707, p=0.0054; Figure 2D), with truncating mutations predominating among non-missense variants. Then, we compared PD-L1 expression between the two groups and found that patients with *SMARCA4* missense mutations had a higher PD-L1 positivity rate (50.27% vs. 35.33%, p=0.0046; Figure 2E), which partially explains the relatively better prognosis observed in this patient subgroup.

3.3. Molecular landscape of *SMARCA4*-mutant LUAD

Comparative analysis of co-occurring genetic alterations between *SMARCA4*-altered tumors (n = 477) and *SMARCA4*-wild-type tumors (n = 5,480) revealed *TP53*, *STK11*, *KEAP1*, *KRAS*, *CDKN2A*, and *EGFR* as the most frequently mutated genes. No statistically significant differences in *TP53* or *KRAS* mutations were observed between the two groups. However, *STK11*, *KEAP1*, and *CDKN2A* mutations were

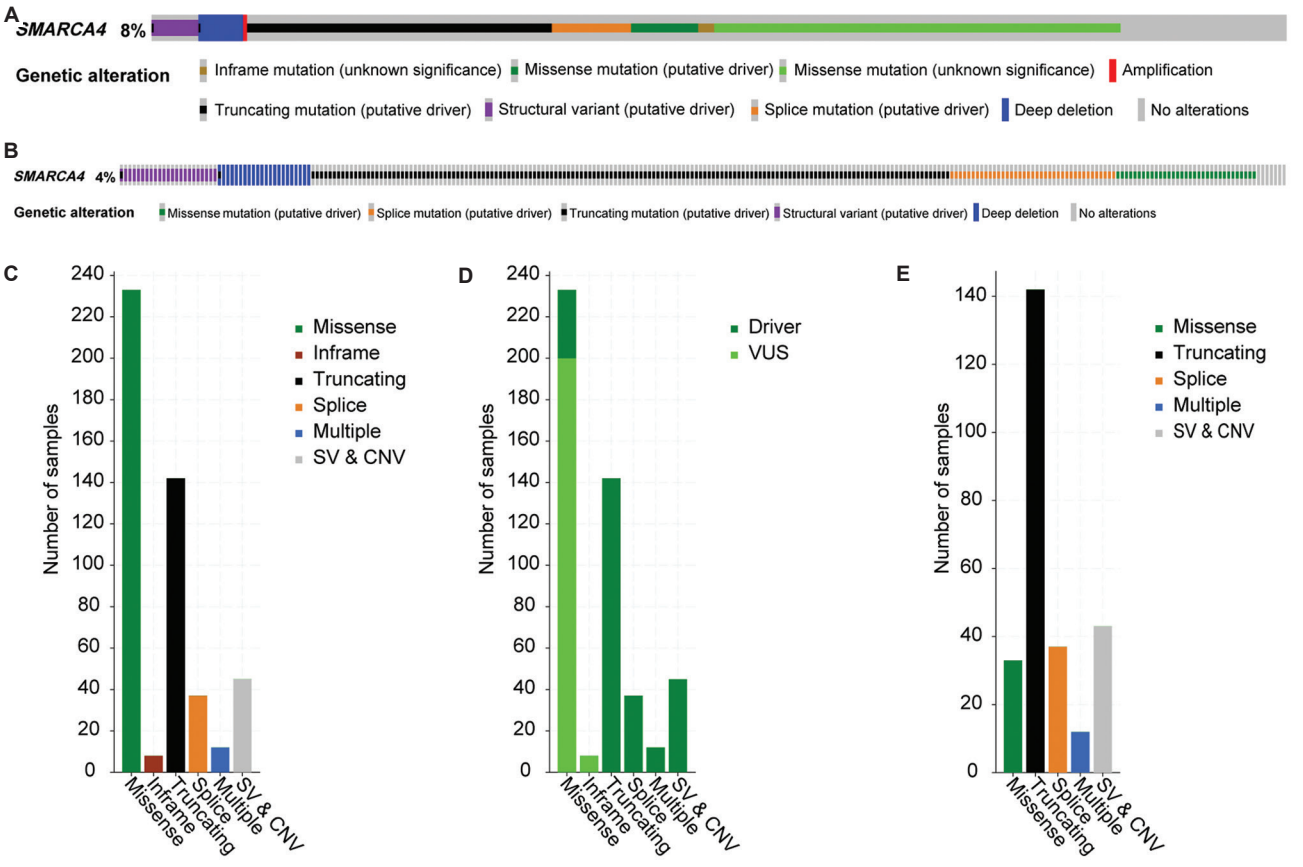

Figure 1. Genomic profiling of *SMARCA4* alterations in LUAD. (A) Mutation frequency of *SMARCA4* in LUAD patients from the Memorial Sloan Kettering Cancer Center-Clinicogenomic Harmonized Oncology Real-world Data (8%, 477/5957). (B) Frequency of *SMARCA4* driver mutations in LUAD (4%, 267/5,957). (C) Proportion of *SMARCA4* mutation types. (D) Variants of unknown significance (VUS) in *SMARCA4* are predominantly missense mutations. (E) Distribution of mutation types among *SMARCA4* driver mutations. Multiple indicates multiple mutation types co-occur.
Abbreviations: CNV: Copy number variation; LUAD: Lung adenocarcinoma; SV: Structural variation.

significantly enriched in *SMARCA4*-altered tumors, whereas *EGFR* alterations were more prevalent in the *SMARCA4*-wild-type group (Figure 3A). Subsequently, we investigated the mutational profiles of the aforementioned common mutated genes and targetable genes (including *ALK*, *ROS1*, *BRAF*, *ERBB2*, *MET*, and *RET*) across the entire LUAD cohort (Figure 3B). Notably, we found that *SMARCA4* mutations were mutually exclusive with alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, *ERBB2*, *MET*, and *RET* in LUAD, a phenomenon suggesting that tumors harboring *SMARCA4* alterations have limited effective targeted therapeutic options available. In addition, we demonstrated the mutation frequencies of these co-mutated genes in *SMARCA4*-altered tumors (Figure 3C): *TP53* (50%), *STK11* (42%), *KEAP1* (42%), *KRAS* (41%), *CDKN2A* (31%), *EGFR* (16%), *ALK* (9%), *BRAF* (8%), *ROS1* (7%), *ERBB2* (6%), *MET* (5%), and *RET* (5%). *TP53* was the most frequently co-mutated gene. Overall, the accompanying mutations in *SMARCA4*-mutant LUAD hold research significance.

3.4. Prognostic impact of *SMARCA4* mutation and common co-mutations in LUAD

We then investigated the impact of *SMARCA4* mutations and common co-mutations (*TP53*, *STK11*, *KEAP1*, *KRAS*, *CDKN2A*, and *EGFR*) alone or in combination on clinical outcomes in LUAD patients. The OS of patients with *SMARCA4*/*TP53* co-mutations was intermediate between those harboring *SMARCA4* or *TP53* mutations alone ($p<0.001$; Figure 4A). Similarly, the same pattern was observed for *EGFR* ($p<0.001$; Figure 4F). Conversely, we found that LUAD patients with co-mutations of *SMARCA4* and *STK11*, *KEAP1*, *KRAS*, or *CDKN2A* exhibited a significantly worse prognosis compared to those with *SMARCA4* mutations alone ($p<0.001$; Figure 4B-E). In summary, these findings suggest that co-mutations in *STK11*, *KEAP1*, *KRAS*, and *CDKN2A* may be associated with the prognosis of *SMARCA4*-mutant LUAD.

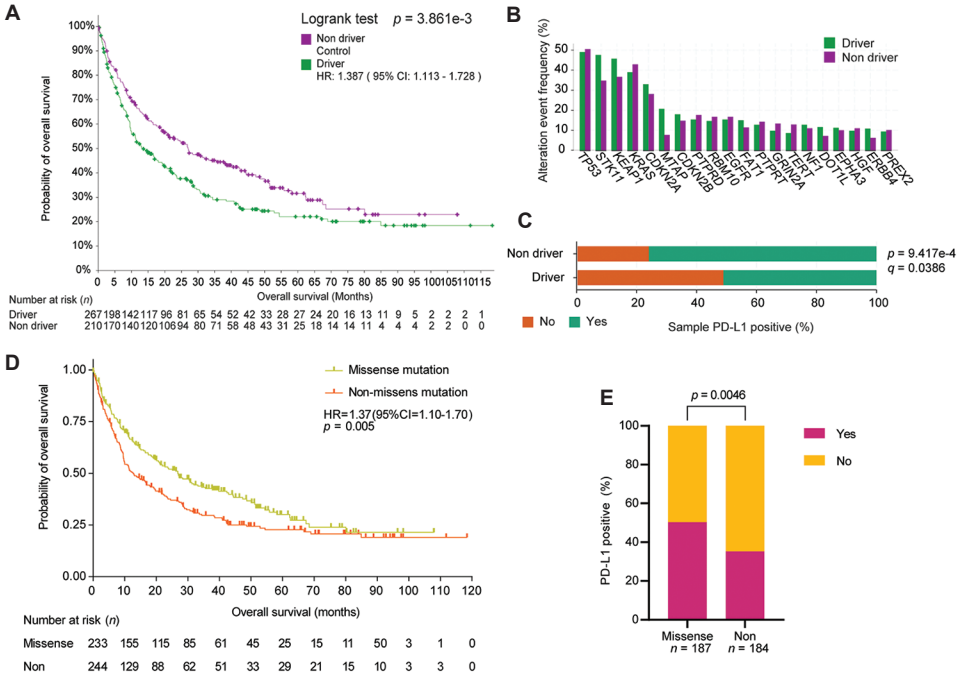

Figure 2. Distinct *SMARCA4* mutation types in LUAD. (A) Prognostic comparison between *SMARCA4* driver and non-driver mutation patients. (B) Co-occurring genetic alterations in *SMARCA4* driver *vs.* non-driver mutation patients. (C) PD-L1 positivity rates in *SMARCA4* driver *vs.* non-driver mutation patients. (D) Prognostic comparison between *SMARCA4* missense and non-missense mutation patients. (E) PD-L1 positivity rates in *SMARCA4* missense *vs.* non-missense mutation patients.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; LUAD: Lung adenocarcinoma; PD-L1: Programmed death-ligand 1.

3.5. Co-mutation patterns and clinical relevance in *SMARCA4*-mutant LUAD

We further investigated the five most frequent co-mutated genes in *SMARCA4*-mutant LUAD. Patients with *EGFR* co-mutations were excluded from the analysis due to the availability of established targeted therapies for this subgroup (n = 76). Co-alterations involving *TP53*, *KRAS*, *STK11*, *KEAP1*, and *CDKN2A* were present in 96% (385/401) of the whole cohort. We then compared the prognosis of patients harboring these five co-mutations and found that their OS was significantly shorter than that of patients without these mutations (p=0.0871; Figure 5B). Furthermore, we observed both co-occurrence and mutual exclusivity patterns among these co-mutated genes (Table 1). *TP53* mutations were mutually exclusive with *KRAS* (p<0.001), *STK11* (p<0.001), *KEAP1* (p<0.001), and *CDKN2A* (p=0.023). Co-occurrence patterns were observed between *STK11* and *KEAP1* (p<0.001), *KRAS* and *STK11* (p<0.001), *KRAS* and *KEAP1* (p<0.001), and *KEAP1* and *CDKN2A* (p=0.006).

To explore the prognostic impact of the interactions among specific co-mutations, we investigated the common co-mutation gene combinations in *SMARCA4*-mutant LUAD. The three most frequently observed clusters were (Figure 5C) (i) *TP53* alone, (ii) *KRAS/STK11/KEAP1*, and (iii) *KRAS/STK11/KEAP1/CDKN2A*. Notably, *STK11/KEAP1* double mutations and *KRAS/STK11/KEAP1* triple mutations were significantly associated with extremely poor OS (median = 6.97 months), whereas patients with *TP53* co-mutations exhibited a relatively favorable prognosis (median OS = 28.96 months) (Figure 5D). Intriguingly, we observed that *SMARCA4*, *KEAP1*, and *STK11* were co-localized on chromosome 19 (Figure 5A).

To further elucidate the prognostic impact and potential mechanisms of distinct co-mutations, we performed analyses focusing on individual co-mutated genes. To exclude the confounding effects of non-immunotherapy-treated patients on prognosis, we selected 195 *SMARCA4*-mutant patients who received immunotherapy (including pembrolizumab, nivolumab, atezolizumab, and durvalumab) for further analysis. Further stratified analysis of the cohort based on *TP53* status (*TP53*-mutant, n = 90 vs. *TP53*-wild-type, n = 105) revealed a statistically significant difference in prognosis between the two groups (median OS: 30.58 months vs. 9.70 months). *TP53*-mutant patients exhibited higher TMB (median TMB: 16.04 vs. 7.78) and higher PD-L1 positivity rates (53.33% vs. 35.24%) than wild-type patients (Figure 5E-G).

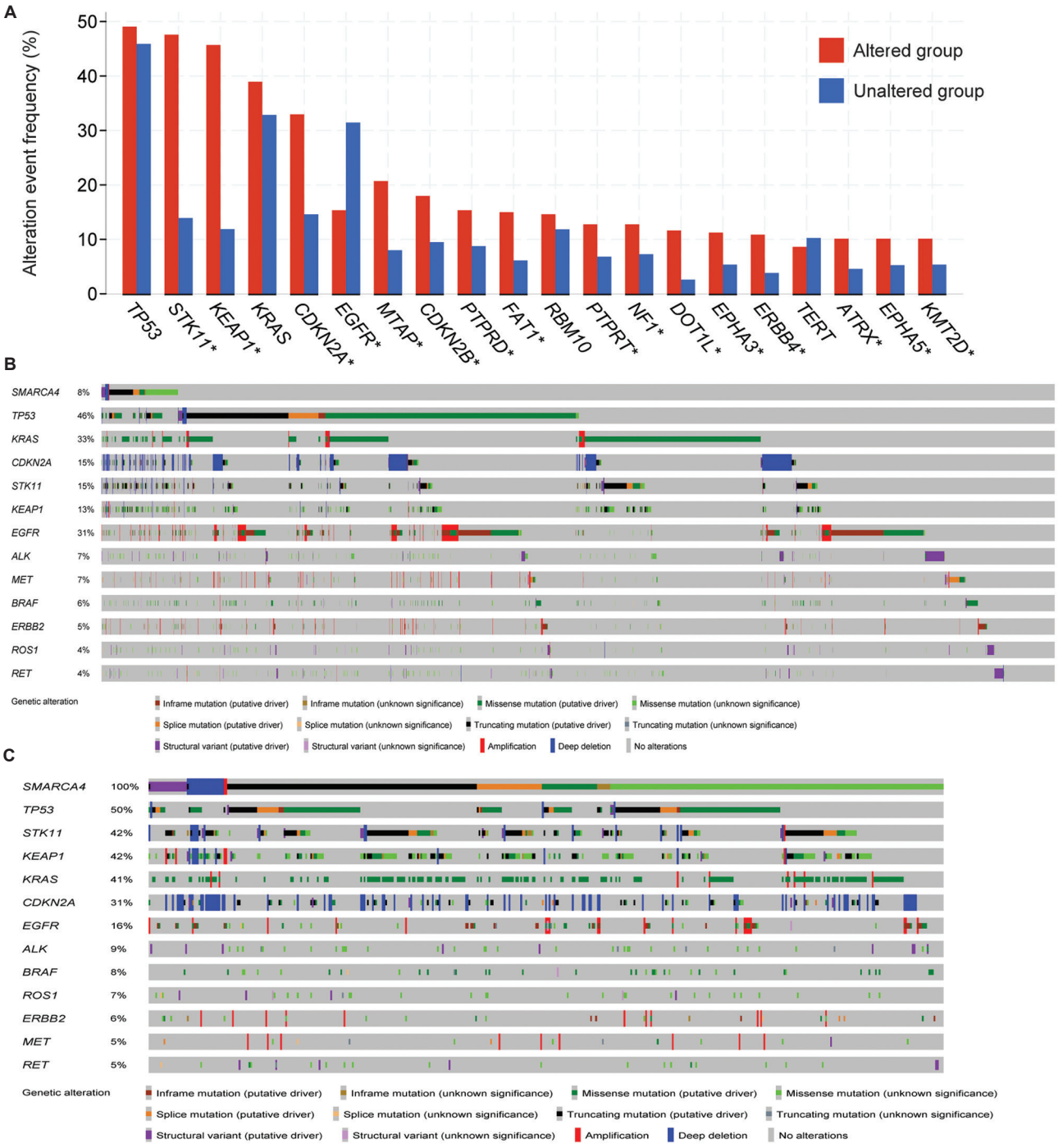

Figure 3. Molecular landscape of *SMARCA4*-mutant lung adenocarcinoma (LUAD). (A) Co-occurring genetic alterations in *SMARCA4*-mutant versus wild-type LUAD patients. (B) Mutual exclusivity between *SMARCA4* mutations and driver alterations (*EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *RET*, *ERBB2*) in LUAD. (C) Mutation frequencies of common co-occurring genes and targetable genes in *SMARCA4*-mutant LUAD patients.

Subsequently, we separately assessed the impact of *KRAS*, *STK11*, *KEAP1*, and *CDKN2A* mutation status on clinical outcomes. Patients in the mutant groups exhibited significantly poorer prognosis compared to those with wild-type alleles: *KRAS* (median OS: 9.99 months vs. 29.62 months, Figure 6A), *STK11* (median OS: 10.68 months vs. 28.41 months; Figure 6B), *KEAP1* (median OS: 8.75 months *vs.* 28.50 months; Figure 6C), and *CDKN2A* (median OS: 12.53 months vs. 20.94 months; Figure 6D). Furthermore, we analyzed the

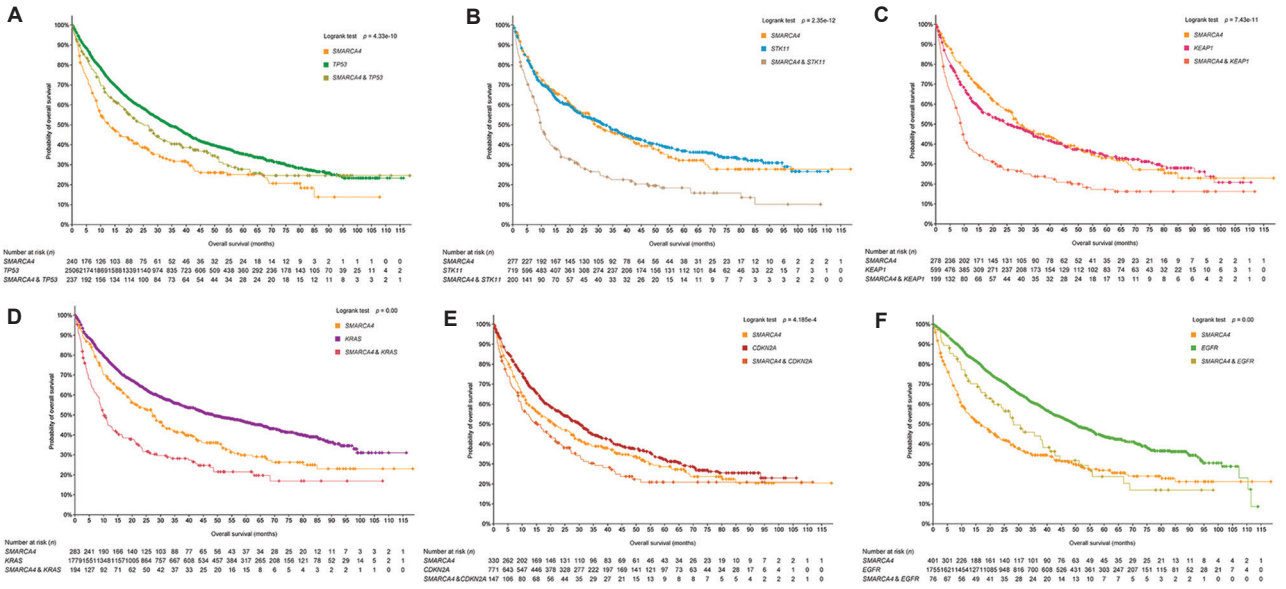

Figure 4. Impact of co-mutations on prognosis in *SMARCA4*-mutant lung adenocarcinoma (LUAD). (A) Prognostic comparison among *SMARCA4*-mutant, *TP53*-mutant, and co-mutant (*SMARCA4*/*TP53*) patients. (B) *STK11*. (C) *KEAP1*. (D) *KRAS*. (E) *CDKN2A*. (F) *EGFR*.

Table 1. The analysis of gene co-occurrence and mutual exclusivity

Gene A	Gene B	Neither	A Not B	B Not A	Both	Log_2 odds ratio	*p*-value	*q*-value	Tendency
STK11	*KEAP1*	163	54	50	134	>3	<0.001*	<0.001	Co-occurrence
TP53	*KRAS*	69	143	143	46	−2.688	<0.001*	<0.001	Mutual exclusivity
TP53	*STK11*	77	136	135	53	−2.17	<0.001*	<0.001	Mutual exclusivity
TP53	*KEAP1*	81	136	131	53	−2.053	<0.001*	<0.001	Mutual exclusivity
KRAS	*STK11*	135	78	77	111	1.319	<0.001*	<0.001	Co-occurrence
KRAS	*KEAP1*	132	85	80	104	1.014	<0.001*	0.001	Co-occurrence
KEAP1	*CDKN2A*	164	115	53	69	0.893	0.006*	0.009	Co-occurrence
TP53	*CDKN2A*	137	142	75	47	−0.726	0.023*	0.029	Mutual exclusivity
STK11	*CDKN2A*	156	123	57	65	0.532	0.103	0.114	Co-occurrence
KRAS	*CDKN2A*	154	125	58	64	0.443	0.16	0.16	Co-occurrence

Note: *indicates statistical significance at $p<0.05$.

impact of co-mutations on TMB and PD-L1 expression. The results are as follows: patients with concurrent *KRAS* mutations exhibited significantly lower TMB compared to *KRAS* wild-type counterparts (median TMB: 8.73 vs. 12.97, $p<0.05$; Figure 6A), while PD-L1 expression showed no intergroup difference (47.12% vs. 39.56%, $p>0.05$; Figure 6A). In contrast, *STK11* (median TMB: 9.02 vs. 11.74, $p>0.05$; Figure 6B) or *KEAP1* (median TMB: 9.02 vs. 11.24, $p>0.05$; Figure 6C) co-mutations were not associated with altered TMB, although the mutant group showed numerically lower values. However, *STK11* (28.09% vs. 56.60%, $p<0.05$; Figure 6B) or *KEAP1* (34.07% vs. 51.92%, $p<0.05$; Figure 6C) mutant tumors demonstrated a lower PD-L1 positivity rate than wild-type tumors. *STK11*/*KEAP1* co-mutations may define an immunogenically cold subset (low TMB and lower PD-L1 positivity rate) within *SMARCA4*-mutant tumors. For *CDKN2A* co-mutation, although the mutant group exhibited lower TMB (median TMB: 9.51 vs. 10.72, $p>0.05$; Figure 6D) and PD-L1 (36.92% vs. 46.92%, $p>0.05$; Figure 6D) levels, these differences were not statistically significant. In summary, these findings suggest that *TP53* as a co-mutated gene is associated with a favorable prognosis in *SMARCA4*-mutant LUAD, while *KRAS*, *STK11*, *KEAP1*, and *CDKN2A* co-mutations may correlate with poorer clinical outcomes.

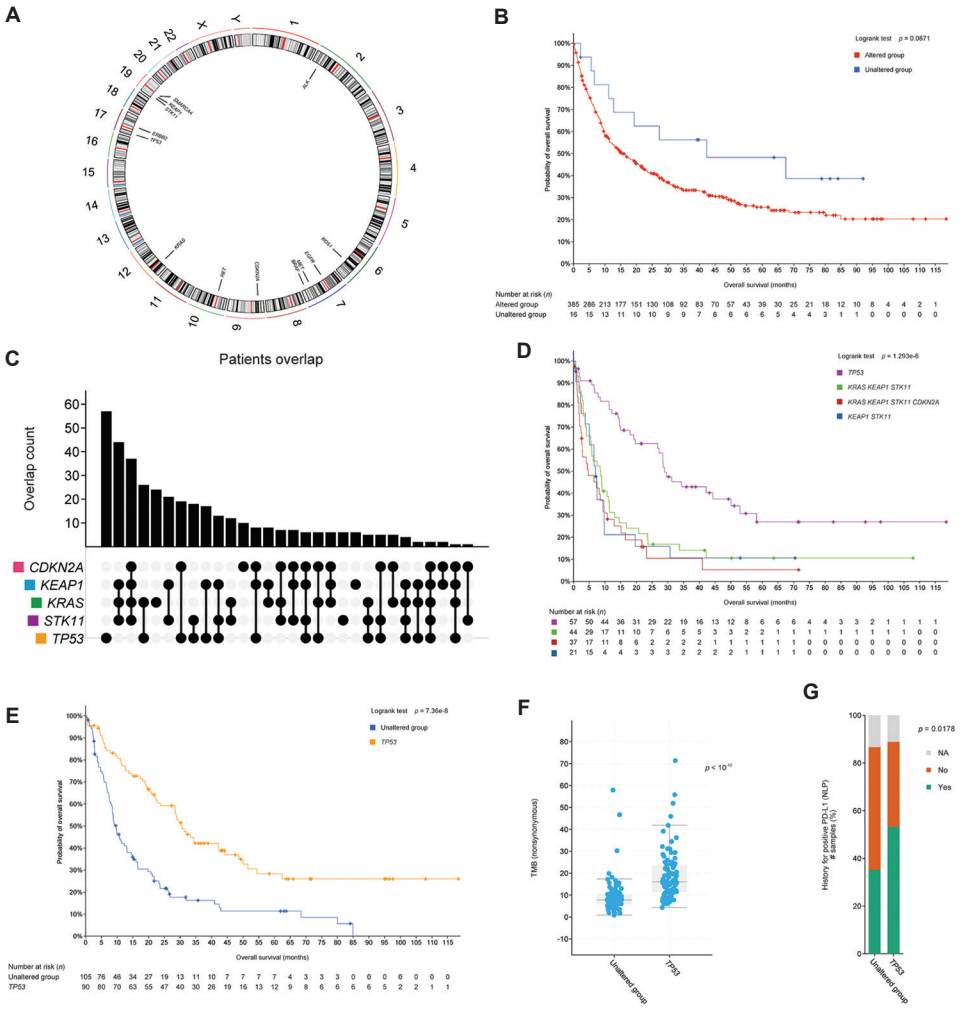

Figure 5. Co-mutation patterns and clinical relevance in *SMARCA4*-mutant LUAD. (A) Chromosomal loci of common co-mutated genes. (B) Prognostic comparison between LUAD patients with common co-mutations (*TP53*, *KRAS*, *STK11*, *KEAP1*, *CDKN2A*) and those without these alterations. (C) Common co-mutation clusters in *SMARCA4*-mutant patients. (D) Prognostic comparison among LUAD patients with distinct co-mutation clusters. (E) Prognostic analysis of 195 immunotherapy-treated *SMARCA4*-mutant patients stratified by *TP53* co-mutation status. (F and G) Higher TMB and elevated PD-L1 expression levels in *SMARCA4*/*TP53* co-mutant patients.
Abbreviations: LUAD: Lung adenocarcinoma; TMB: Tumor mutational burden; PD-L1: Programmed death-ligand 1.

3.6. *KRAS*, *STK11*, and *KEAP1* mutations are independent prognostic factors in *SMARCA4*-mutant LUAD

To evaluate the specific impact of individual co-mutated genes on clinical outcomes while accounting for the heterogeneity of coexisting alterations, we performed both univariable and multivariable Cox proportional hazards analyses. Each co-mutated gene (*TP53*, *KRAS*, *STK11*, *KEAP1*, and *CDKN2A*) was initially assessed independently to identify its unadjusted association with survival endpoints (OS). HR with 95% CI was calculated to quantify the risk magnitude. Univariable Cox analysis identified clinical stage (HR = 1.882, $p<0.001$) and mutations in *TP53* (HR = 0.627, $p<0.001$), *KRAS* (HR = 1.543, $p<0.001$), *STK11* (HR = 1.873, $p<0.001$), *KEAP1* (HR = 2.076, $p<0.001$), and *CDKN2A* (HR = 1.306, $p=0.041$) as significant prognostic factors in *SMARCA4*-mutant LUAD (Figure 7A). To isolate the independent prognostic effect of each gene, we constructed multivariable models adjusting for clinically relevant confounders, including tumor stage (Stage IV vs. Stage I–III) and significant co-mutations (*TP53*, *KRAS*, *STK11*, *KEAP1*, and *CDKN2A*). Multivariable Cox regression confirmed clinical stage (HR = 1.968, $p<0.001$), *KRAS* (HR = 1.350, $p=0.029$), *STK11* (HR = 1.342, $p=0.045$), and *KEAP1* (HR = 1.703, $p<0.001$) as independent prognostic factors (Figure 7B).

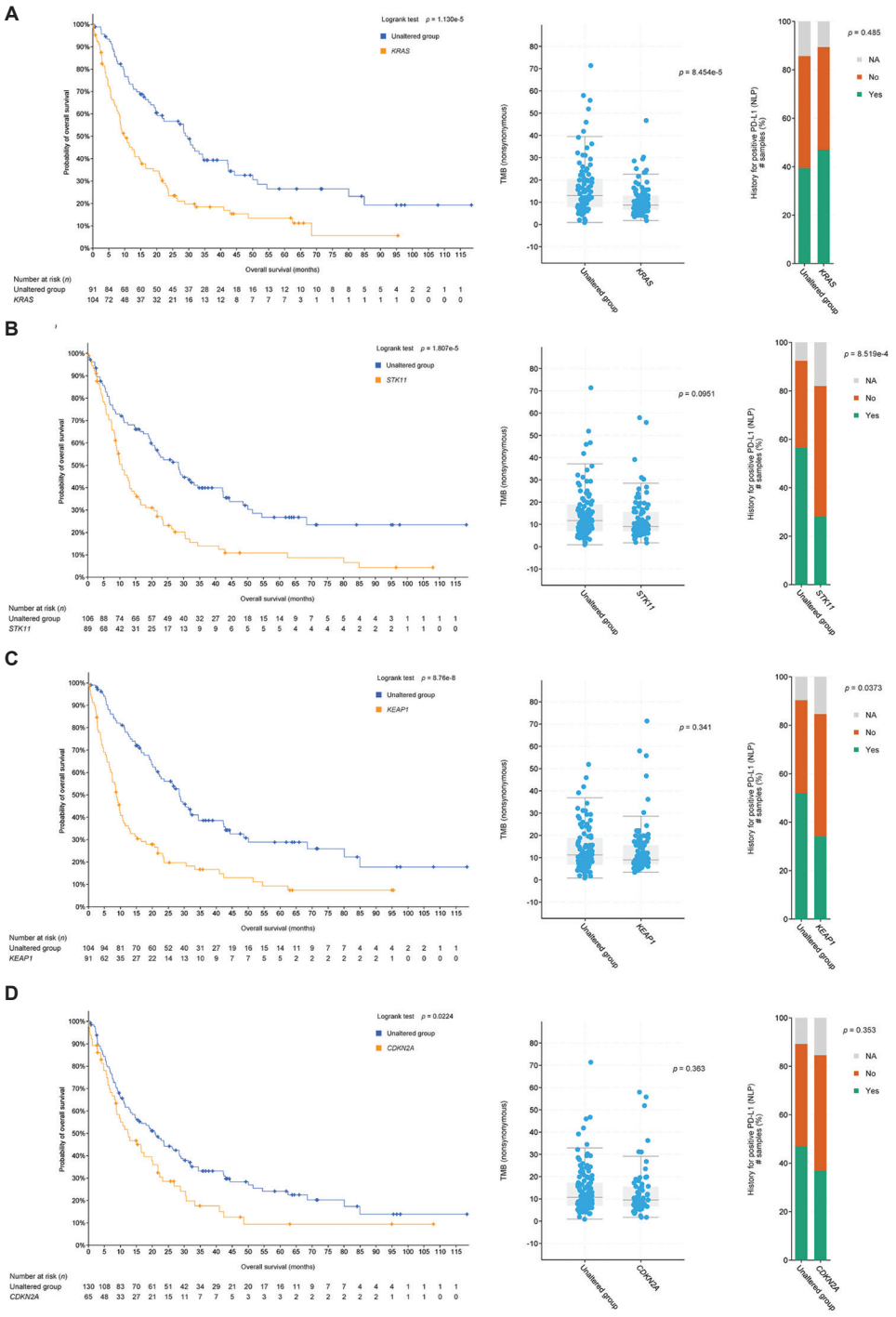

Figure 6. Overall survival, tumor mutational burden, and programmed death-ligand 1 expression outcomes. (A) Stratified by *KRAS* co-mutation status, (B) by *STK11*, (C) by *KEAP1*, and (D) by *CDKN2A*.

Interestingly, we observed that *TP53* mutations were associated with a protective effect (HR < 1), although this association did not reach statistical significance in multivariable analysis (p=0.221).

3.7. *TP53* and *KRAS* co-mutations correlate with immunotherapy benefit

Finally, we evaluated whether co-mutation profiles predict differential responses to immunotherapy in

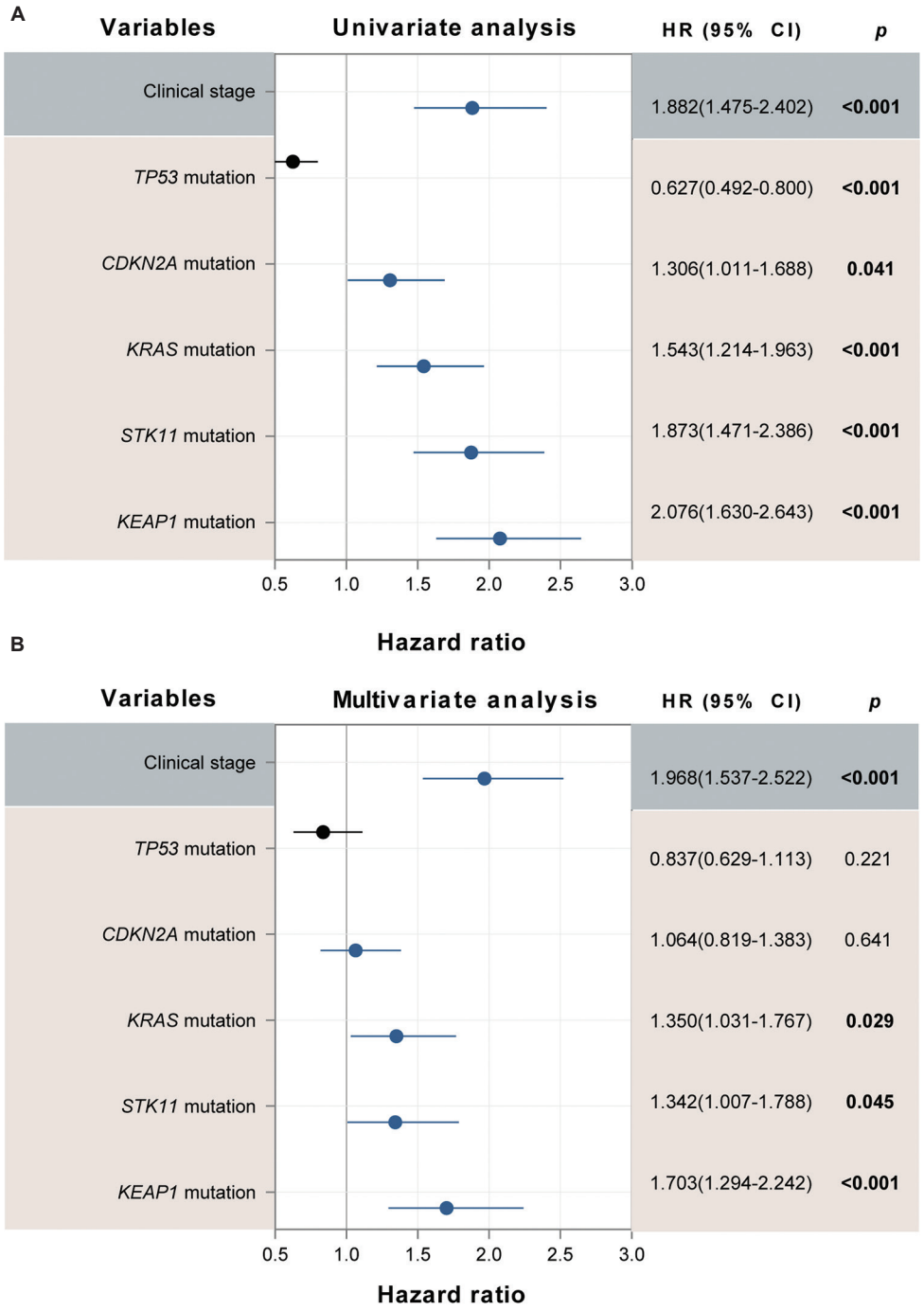

Figure 7. Univariate and multivariate analysis. (A) Univariate analysis of overall survival in patients with *SMARCA4*-mutant LUAD. (B) Multivariate analysis of overall survival in patients with *SMARCA4*-mutant LUAD. Note: Boldface indicates statistical significance.
Abbreviations: CI: Confidence interval; HR: Hazard ratio; LUAD: Lung adenocarcinoma.

SMARCA4-mutant LUAD. We also compared survival outcomes using Kaplan–Meier analysis with log-rank tests. In patients with *TP53* co-mutations, the use of immune checkpoint inhibitors (ICIs) was associated with significantly improved survival (median OS: 28.96 months vs. 8.61 months, HR: 0.5317, 95% CI: 0.3113–0.9084, p=0.0088; Figure 8A). Similarly, ICIs treatment also demonstrated a significant survival benefit in *KRAS* co-mutant patients (median OS: 8.614 months vs. 2.548 months, HR: 0.4911, 95% CI: 0.2959–0.8151,

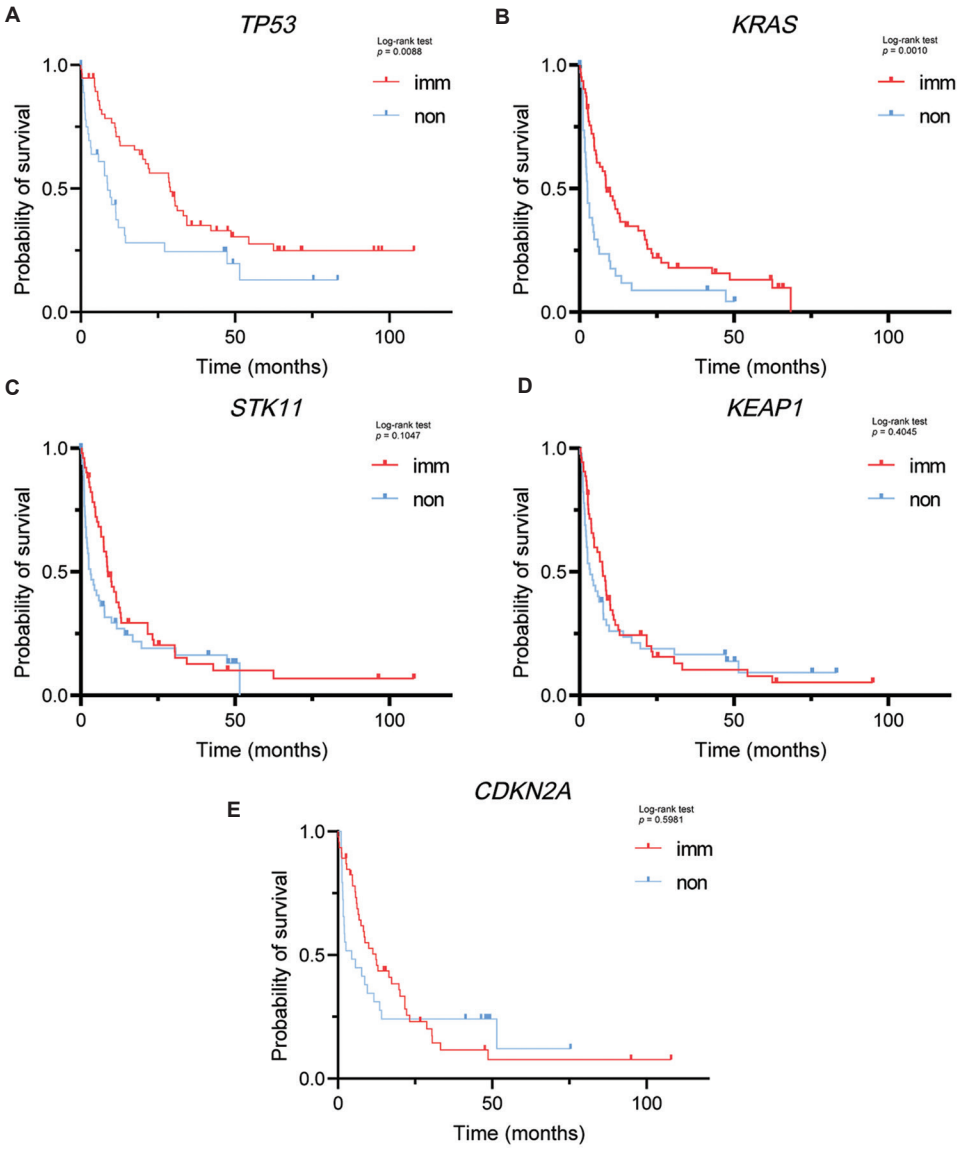

Figure 8. Impact of co-mutations on immunotherapy efficacy in *SMARCA4*-mutant LUAD. (A) Prognostic comparison in Stage IV *SMARCA4*-mutant patients with concurrent *TP53* mutations, stratified by immunotherapy receipt, (B) with concurrent *KRAS* mutations, (C) with concurrent *KEAP1* mutations, (D) with concurrent *STK11* mutations, and (E) with concurrent *CDKN2A* mutations.
Abbreviation: Imm: Immunotherapy.

p=0.0010; Figure 8B). However, in patients with *STK11* (*p*=0.1047; Figure 8C), *KEAP1* (*p*=0.4045; Figure 8D), or *CDKN2A* (*p*=0.5981; Figure 8E) mutations, there was no significant difference in survival outcomes between those who received ICIs therapy and those who did not.

4. Discussion

SMRACA4-mutant LUAD has garnered significant clinical attention due to their association with poor prognosis, though this paradigm may be reshaped by distinct co-mutation profiles. Advances in NGS have deepened our understanding of tumor genetic landscapes, and genomic profiling has become integral to cancer diagnosis and treatment in the era of precision medicine. However, the inherent heterogeneity of *SMRACA4*-mutant LUAD leads to marked interpatient variability in response to ICIs. The clinical translation of effective biomarkers and molecular subtyping remains a critical barrier to optimizing therapeutic strategies. Consequently, identifying robust biomarkers for patient stratification is imperative to select ICI-sensitive subgroups. Further refinement of molecular classification systems based on co-mutation signatures will

enhance prognostic prediction and guide personalized immunotherapy regimens for *SMRACA4*-mutant LUAD patients.

In this study, the most frequently co-mutated genes in *SMARCA4*-mutant LUAD were *TP53*, *STK11*, *KEAP1*, *KRAS*, and *CDKN2A*. There was minimal overlap between *SMARCA4* mutations and actionable oncogenic driver alterations such as *EGFR* and *ALK*. Previous studies have shown that *SMARCA4*-mutant lung cancers may be more sensitive to immunotherapy.[15,22,23] In contrast, other studies suggest that tumors with *SMARCA4* variants did not exhibit a survival benefit on immunotherapy.[18,19,24,25] These findings indicate that the clinical heterogeneity observed in *SMARCA4*-mutant LUAD patients may stem from divergent coexisting molecular events. According to previous studies, *KRAS* and *TP53* mutations are established adverse prognostic factors in NSCLC.[26-29] However, advancements in ICIs may alter the clinical course of these co-mutant tumors. Notably, emerging evidence indicates that *KRAS* and *TP53* mutations correlate with elevated PD-L1 expression and enhanced ICIs responses in LUAD,[30,31] a pattern consistent with our observations. A case report documented sustained clinical benefit in a patient with thoracic lung cancer and *TP53* mutations treated with combination immunotherapy.[32] Mechanistically, *TP53* alterations are known to induce genomic instability,[33] a feature increasingly linked to enhanced ICI responsiveness.[34] This phenomenon may be mediated through elevated TMB, which generates immunogenic neoantigens. Notably, TMB has emerged as an independent biomarker of ICIs response, with high TMB levels strongly correlating with improved prognosis in NSCLC patients receiving PD-L1 inhibitors.[35] Conversely, accumulating evidence links *KEAP1* and *STK11* mutations to inferior prognosis,[36,37] with studies demonstrating that concurrent *STK11* alterations may drive resistance to ICIs.[6,38] Similarly, *KEAP1* aberrations are associated with diminished immunotherapy responsiveness.[39] The underlying mechanisms may be linked to a low tumor microenvironment-related signature in these patients.[40,41] In brief, mutations in *STK11* and *KEAP1* are associated with resistance to immunotherapy, suggesting that *SMARCA4*-mutant LUAD harboring co-mutations in these genes may similarly be refractory to treatment. LUA has a high mutation rate. Therefore, when evaluating *SMARCA4* as a predictive biomarker for ICIs' efficacy, it is imperative to rigorously account for coexisting mutations that may confound therapeutic outcomes.

The findings of this study reveal distinct prognostic and therapeutic implications associated with specific genomic alterations in *SMARCA4*-mutant LUAD. Our analysis suggests that *TP53* mutations are correlated with a relatively favorable prognosis, whereas *KRAS*, *STK11*, and *KEAP1* mutations are independent prognostic factors. Notably, these genetic alterations also exhibit divergent associations with immunotherapy efficacy, highlighting their potential as biomarkers for personalized treatment strategies.

TP53 mutations were associated with improved OS in this cohort, a finding that contrasts with some prior studies linking *TP53* dysfunction to aggressive tumor behavior.[42,43] This apparent paradox may stem from the dual role of *TP53* in both tumor suppression and modulation of the tumor microenvironment. Recent evidence suggests that *TP53* loss can enhance immunogenicity by increasing TMB or promoting neoantigen presentation,[44,45] thereby sensitizing tumors to ICIs. In our analysis, *TP53*-mutant tumors demonstrated higher PD-L1 expression and TMB compared to wild-type counterparts, potentially explaining the superior immunotherapy outcomes observed in this subgroup. However, the lack of statistical significance in multivariable analysis (p=0.221) underscores the need to explore confounding factors, such as coexisting alterations, treatment heterogeneity, and *TP53* mutation heterogeneity, which may obscure the independent prognostic value of *TP53*. Previous studies suggest that the prognostic value of *TP53* mutations may vary by mutation type (e.g., missense, nonsense, frameshift).[46] For instance, certain missense mutations may retain partial TP53 function, whereas nonsense mutations cause complete protein truncation, potentially eliciting divergent impacts on the tumor immune microenvironment. In this study, *TP53* mutations were analyzed collectively without subtype stratification, which may mask the significant effects of specific variants and contribute to the non-significant association observed in multivariable models (HR = 0.837, p=0.221). Future investigations should expand cohort sizes and incorporate *TP53* mutational subtypes to validate their stability in prognostic frameworks.

KRAS mutations, long recognized as drivers of oncogenic signaling and poor prognosis, paradoxically correlated with enhanced ICIs efficacy in our study. This aligns with previous evidence that *KRAS*-driven tumors may foster an inflammatory tumor microenvironment characterized by upregulated PD-L1 expression and $CD8^+$ T-cell infiltration.[30] Nevertheless, the coexistence of *KRAS* with *STK11* or *KEAP1* mutations, a common phenomenon in LUAD, may abrogate this benefit, as these alterations are known to suppress antitumor immunity through metabolic reprogramming and reductase-oxidative activity.[47]

In contrast to *TP53* and *KRAS*, *STK11* and *KEAP1* mutations were robustly associated with reduced survival

and inferior immunotherapy response. *STK11* loss promotes a metabolically cold tumor microenvironment marked by reduced T-cell infiltration and PD-L1 expression.[48] Similarly, *KEAP1* mutations dysregulate the nuclear factor erythroid 2-related factor 2 pathway, fostering a state that enhances tumor cell survival while suppressing immune recognition.[49] These mechanisms likely explain the significantly lower PD-L1 positivity rates and TMB observed in *STK11*/*KEAP1*-mutant tumors in our cohort. Intriguingly, the mutual exclusivity of *TP53* with *STK11*/*KEAP1* mutations contrasts sharply with the near-synonymous co-alteration of *STK11* and *KEAP1* (Table 1). This dichotomy likely stems from the genomic architecture of chromosome 19p13.2,[50] which harbors *SMARCA4*, *STK11*, and *KEAP1*. Large-scale deletions or epigenetic silencing in this region may simultaneously inactivate these genes, fostering a storm of metabolic dysregulation (*STK11*/*KEAP1* loss) and chromatin instability (*SMARCA4* deficiency). Conversely, *TP53* mutations may define an alternate evolutionary trajectory, bypassing the need for 19p13.2 alterations. The underlying mechanism of this phenomenon is closely associated with the functional antagonism between the two gene groups in regulating tumor genomic stability, metabolic reprogramming, and immune microenvironment. *TP53* mutations promote cell proliferation by abrogating cell-cycle checkpoints, whereas *STK11*/*KEAP1* mutations sustain cell survival through metabolic reprogramming (e.g., enhanced glycolysis and glutaminolysis). These two pathways support tumorigenesis through proliferation-driven and metabolic adaptation mechanisms, respectively, rendering cells less likely to rely on both simultaneously, thus favoring the retention of a single mutational pattern. Furthermore, *TP53* and *STK11*/*KEAP1* mutations differentially modulate tumor immunogenicity and the immune microenvironment, leading to distinct responses to ICIs. Genomic instability induced by *TP53* mutations significantly increases TMB, while loss of *TP53* function upregulates PD-L1 expression, thereby enhancing the efficacy of ICIs by increasing target engagement.[31] In addition, *TP53* mutations may promote regulatory T-cell infiltration, creating an immunosuppressive tumor microenvironment,[51] which suggests that immunotherapeutic strategies could be particularly beneficial for this molecularly defined subset of patients. In contrast, *STK11*/*KEAP1* mutations remodel the tumor microenvironment into an immunosuppressive phenotype through multiple mechanisms that undermine ICI responses, including reduced PD-L1 expression, diminished chemokine signaling, and attenuated T-cell activation.[13,38,48,52]

In summary, our findings underscore the importance of integrating molecular profiling into clinical decision-making. These co-mutated genes could guide risk stratification and personalized therapeutic strategies in *SMARCA4*-mutant LUAD. Our analysis indicates that *TP53* co-mutation may be a protective factor and that patients with *TP53* mutations should initiate immunotherapy as early as possible. *STK11*/*KEAP1* alterations identify a high-risk population requiring alternative therapeutic strategies to overcome intrinsic immunotherapy resistance. Patients with *STK11*/*KEAP1* mutations require intensified follow-up, should avoid ICI monotherapy, and prioritize the use of chemotherapy combined with anti-angiogenic agents. Instead, these patients might benefit from combinatorial strategies targeting metabolic vulnerabilities (e.g., glutaminase inhibitors[53-55]) or from augmenting immune activation (e.g., stimulator of interferon genes agonists[56]). While *KRAS* mutations may identify patients likely to benefit from ICIs, co-occurring *KRAS* mutations with *STK11* or *KEAP1* are associated with a worse prognosis. Thus, the clinical utility of *KRAS* as a standalone biomarker warrants cautious interpretation and necessitates combinatorial genomic profiling.

Critically, our study transcends mere molecular characterization by establishing the direct clinical utility of co-mutation patterns in *SMARCA4*-mutant LUAD. The identification of three prognostically distinct co-mutation clusters, (i) immunogenic (*SMARCA4*/*TP53*), (ii) metabolically immunosuppressive (*SMARCA4*/*STK11*/*KEAP1*), and (iii) kinase-driven (*SMARCA4*/*KRAS*), provides an actionable framework for personalized therapeutic stratification. For prognostic stratification, the 4.15-fold difference in median OS between *SMARCA4*/*TP53* (28.96 months) and *SMARCA4*/*STK11*/*KEAP1* (6.97 months) cohorts ($p<0.001$) underscores the imperative to abandon "one-size-fits-all" approaches for *SMARCA4*-altered LUAD. For therapeutic guidance, *SMARCA4*/*TP53* mutant tumors should be prioritized for frontline immunotherapy, leveraging their high TMB and PD-L1 positivity. *SMARCA4*/*STK11*/*KEAP1* mutant tumors warrant trials combining ICIs with metabolic modulators (e.g., glutaminase inhibitors) to reverse drug resistance reactions. *SMARCA4*/*KRAS* mutant tumors may benefit from novel Kirsten rat sarcoma viral oncogene homolog inhibitors (e.g., sotorasib) and programmed cell death protein 1 blockade to target both oncogenic signaling and immune evasion. For diagnostic implications, integrating co-mutation profiling into routine NGS panels (*SMARCA4*, *TP53*, *STK11*, *KEAP1*, *KRAS*, and *CDKN2A*) could optimize risk stratification at a minimal added cost. Furthermore, these findings have immediate implications for clinical trial designs.

This study has certain limitations. First, it adopted a retrospective design, using data from prior clinical records

and test results, which inevitably introduced biases into the information collection. In addition, there is a lack of analysis on epigenetic changes, and insufficient data on objective response rate and progression-free survival in the immunotherapy group. Second, potential selection bias may affect the extrapolation of the conclusions: all enrolled patients are cases that have undergone genomic testing and have completed follow-up data. However, in clinical practice, some advanced-stage patients did not undergo testing due to rapid progression or were lost to follow-up. The absence of such populations may bias the sample toward subgroups with better prognoses, thereby weakening the study's representativeness of the broader real-world population. Third, the current mechanism analysis is mainly based on the correlation of clinical data and literature inference, lacking *in vivo* and *in vitro* functional experimental verification. For example, the mutual exclusivity of *TP53* and *STK11*/*KEAP1* mutations and their regulatory effects on the immune microenvironment have not been directly confirmed using gene-edited cell models or animal experiments, and the molecular-level causal relationships remain to be further verified. Furthermore, our conclusions require validation in larger, multi-institutional cohorts and prospective clinical trials to refine stratification models. Systematically dissecting how specific co-mutations (e.g., *SMARCA4*/*TP53 vs. SMARCA4*/*STK11*/*KEAP1*) diversify clinical outcomes through *in vitro* and *in vivo* models. In the future, co-mutations should be included in the *SMARCA4*-mutant lung cancer precision therapy stratification criteria, and biomarker frameworks should integrate composite genomic signatures (e.g., *SMARCA4*$^{+}$/*STK11*$^{-}$/*KEAP1*$^{-}$) rather than relying on single-gene alterations to guide prognosis evaluation and therapeutic decision-making.

5. Conclusion

In *SMARCA4*-mutant LUAD patients, *TP53*, *STK11*, *KEAP1*, *KRAS*, and *CDKN2A* emerged as the most prevalent co-occurring genomic alterations. Notably, *TP53* mutations exhibited mutual exclusivity with *KRAS*, *STK11*, and *KEAP1* alterations, suggesting divergent oncogenic trajectories. Multivariable analysis identified *KRAS*, *STK11*, and *KEAP1* co-mutations as independent adverse prognostic factors. Conversely, *TP53* co-mutations correlated with favorable outcomes and enhanced immunotherapy efficacy, likely attributable to elevated TMB and PD-L1 expression in this subgroup. Collectively, our findings underscore that distinct mutational landscapes dictate prognosis in *SMARCA4*-driven LUAD, advocating for co-mutation-guided therapeutic stratification.

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Conflict of interest

The authors declare that they have no competing financial interests or personal relationships.

Author contributions

Conceptualization: Yifan Xu
Formal analysis: Yufeng Li
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Writing–original draft: Yufeng Li
Writing–review & editing: Zhipeng Wei, Yifan Xu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data generated in the present study may be requested from the corresponding author.

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