The Genomic Landscape of *SMARCA4* Alterations and Associations with Outcomes in Patients with Lung Cancer

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ABSTRACT

Purpose: *SMARCA4* mutations are among the most common recurrent alterations in non–small cell lung cancer (NSCLC), but the relationship to other genomic abnormalities and clinical impact has not been established.

Experimental Design: To characterize *SMARCA4* alterations in NSCLC, we analyzed the genomic, protein expression, and clinical outcome data of patients with *SMARCA4* alterations treated at Memorial Sloan Kettering.

Results: In 4,813 tumors from patients with NSCLC, we identified 8% ($n = 407$) of patients with *SMARCA4*-mutant lung cancer. We describe two categories of *SMARCA4* mutations: class 1 mutations (truncating mutations, fusions, and homozygous deletion) and class 2 mutations (missense mutations). Protein expression loss was associated with class 1 mutation (81% vs. 0%, $P < 0.001$). Both classes of mutation co-occurred more frequently with *KRAS, STK11*, and *KEAP1* mutations compared with *SMARCA4* wild-type tumors ($P < 0.001$). In patients with metastatic NSCLC, *SMARCA4* alterations were associated with shorter overall survival, with class 1 alterations associated with shortest survival times ($P < 0.001$). Conversely, we found that treatment with immune checkpoint inhibitors (ICI) was associated with improved outcomes in patients with *SMARCA4*-mutant tumors ($P = 0.01$), with class 1 mutations having the best response to ICIs ($P = 0.027$).

Conclusions: *SMARCA4* alterations can be divided into two clinically relevant genomic classes associated with differential protein expression as well as distinct prognostic and treatment implications. Both classes co-occur with *KEAP1, STK11*, and *KRAS* mutations, but individually represent independent predictors of poor prognosis. Despite association with poor outcomes, *SMARCA4*-mutant lung cancers may be more sensitive to immunotherapy.

Introduction

Genomic abnormalities in the subunits of the *SWI/SNF* chromatin remodeling complex occur in approximately 20% of solid tumors, and emerging data suggest that specific alterations within this complex might affect outcomes in certain solid tumors (1–3). For example, alterations in the SWI/SNF complex gene *PBRM1* have been associated with improved outcomes in patients with renal cell carcinoma treated with immune checkpoint inhibitors (ICI; refs. 3, 4). In lung cancer, inactivation of the catalytic subunit SMARCA4 (BRG1) is the most common alteration within the SWI/SNF complex and has been associated with poor patient outcomes (1, 5–10). SMARCA4 is one of two mutually exclusive DNA-dependent ATPases, along with SMARCA2, involved in transcriptional regulation of gene expression (11, 12). Yet, the relationship between *SMARCA4* and other alterations within the complex genomic landscape of lung cancer remains unclear.

Multiple studies have recently highlighted the importance of considering genes of interest within the context of commonly co-occurring mutations (13–18). For example, the identification of *STK11*-, *KEAP1*-, and *TP53*-mutant subgroups has changed the paradigm of classifying *KRAS*-mutant lung cancers and non–small cell lung cancers (NSCLCs) in general (13–15, 18). These distinct subgroups correlate with differential responses to immunotherapy and long-term outcomes (13, 14, 17, 18). Further, in *EGFR*-mutant lung cancer, mutations in *TP53* and *RB1* are associated with shorter response to tyrosine kinase inhibitors and transformation to small cell carcinoma (15, 16). Previous studies have shown that *SMARCA4* alterations can co-occur in *KRAS*-mutant tumors, yet they also occur independently and less commonly with other driver oncogenes such as *EGFR* (5, 6).

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Translational Relevance

In this study, we characterize the clinical, molecular, and histologic relationships of *SMARCA4* genomic and protein alterations in lung cancer. *SMARCA4* is the most commonly mutated member of the SWI/SNF complex, with mutations occurring in 8% of patients with non–small cell lung cancer. Genomic, protein expression, and clinical outcome data identify two distinct classes of *SMARCA4* alterations. *SMARCA4* alterations often co-occur with *STK11, KEAP1*, and *KRAS* alterations, but they are a prognostic factor, independent of these alterations. Although patients whose tumors have class 1 *SMARCA4* alterations (associated with protein expression loss) have a very poor prognosis, they may have higher response rates to PD-(L)1 blockade despite low PD-L1 expression.

However, there are only limited data on *SMARCA4's* relationship to these other co-occurring mutations (8, 10), and the significance of *SMARCA4* alterations among oncogene-driven subsets of lung cancer is unknown.

Increased understanding of the relationship of *SMARCA4* in lung cancer may enable new therapeutic opportunities in the future. Recently, *SMARCA4* alterations have been shown to be oncogenic drivers in a highly aggressive subset of ovarian cancer, small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) that shows increased susceptibility to ICIs (19). Further, there have been case reports of durable responses to ICIs in thoracic *SMARCA4*-deficient undifferentiated tumors and *SMARCA4*-deficient lung carcinoma (20, 21), but no studies have comprehensively evaluated treatment outcomes in a large cohort of patients with lung cancer. In this study, we characterize the clinical, molecular, and histologic relationships of *SMARCA4* genomic and protein alterations in lung cancer.

Materials and Methods

We identified all patients with NSCLC of any stage with *SMARCA4* alterations detected by MSK-IMPACT NGS (22) until April of 2019 who were treated at Memorial Sloan Kettering Cancer Center (MSK) for genomic analysis (Supplementary **Fig. S1**).

SMARCA4 alterations were classified into two groups: (i) *SMARCA4* truncating mutations, fusions, and homozygous deletions were deemed "class 1 alteration" and (ii) *SMARCA4* missense mutations or variants of unknown significance, or "class 2 alteration" based upon categorization in OncoKB (23). Tumors with concurrent class 1 and class 2 alterations were classified within the class 1 category. A retrospective pathologic analysis of expression of SMARCA4 in all cases of with *SMARCA4* molecular alterations was performed by IHC using the previously described methods (10).

Somatic alterations were identified using the MSK-IMPACT assay as previously described (22). Individual genes were queried for distribution and enrichment among the patients with and without *SMARCA4* alterations. Frequencies of gene alterations by *SMARCA4* alteration were considered significant with a P value < 0.05 and, to reduce false discovery in multiple testing, FDR q value < 0.10. Tumor mutation burden (TMB) was normalized across each version of the MSK-IMPACT panel (341, 410, or 468 genes) and defined as the total number of mutations divided by the coding region captured reported as mutations/megabase in each panel [0.897 megabases (Mb) for 341-, 1.017 Mb for 410-, and 1.139 Mb for 468-gene panel]. PD-L1 expression was scored as the percentage of tumor cells with membranous staining using predominantly E1L3N antibody, as previously described (24).

Medical, pharmacy, and pathology records for all patients with metastatic NSCLC and *SMARCA4* alterations were reviewed to collect demographic, pathologic, and treatment data. A random sample of patients with metastatic NSCLC who had MSK-IMPACT without *SMARCA4* alterations and were tested during the same time period was used as a comparator group. The response to anti–PD-(L)1 therapy was determined (database lock of April 1, 2019) using RECIST version 1.1. by thoracic radiologists. This study was approved by the Institutional Review Board/Privacy Board at MSK and was in accordance with the Belmont report for retrospective review of records and waiver of consent.

Statistical methods

Patient and tumor characteristics were compared across S*MARCA4* mutation classes (class 1, class 2, wild-type) using χ^2 tests and Kruskal–Wallis tests. Overall survival (OS) defined from the date of metastatic diagnosis to death and accounted for the left truncation time from metastatic diagnosis to IMPACT biopsy. Patients without events were censored at their last known visit date. Survival curves and estimates of the median survival time were generated using Kaplan–Meier methods and compared across the three mutation classes using log-rank tests. A Cox proportional hazards model was adjusted for age, sex, smoking status (never smoker, former light smoker, former heavy smoker, and current smoker), histology (adenocarcinoma, squamous, other), as well as co-occurring *STK11* and *KEAP1* mutations, and TMB. HR and 95% confidence intervals (CIs) are reported. Subanalyses of OS were performed among patients with *KRAS* mutations. Patients without follow-up after their IMPACT pathology date were excluded from analyses ($n = 5$).

The response to immunotherapy as characterized by progression-free survival (PFS), OS, and overall response rate (ORR) was examined among the subset of patients that received immunotherapy. PFS was defined as the time from start of PD-(L)1 inhibitor to clinical or radiographic progression, death, or the end of follow-up, and OS was defined as the time from the start of PD-(L)1 inhibitor to death or the end of follow-up. PFS and OS were analyzed using Kaplan–Meier methods and Cox proportional hazards model accounting for left truncation, again adjusted for age, sex, smoking status, histology, TMB, and co-occurring *STK11* and *KEAP1* mutations. Best overall response was defined as complete or partial response. Multivariable logistic regression was applied to compare the likelihood of ORR across *SMARCA4* mutation classes adjusted for age, TMB, PD-L1, *STK11*, and *KEAP1*.

To assess whether immunotherapy is associated with improved survival among patients with class 1 or 2 *SMARCA4* mutations, we first calculated the propensity score and probability of receipt of ICIs based on available variables (mutation class, age, sex, race, smoking status, histology, TMB, and co-occurring *STK11* and *KEAP1* mutations). We then adjusted for the propensity score when comparing OS for patients that received ICIs versus patients that did not via a Cox proportional hazards model accounting for left truncation. A P value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed with GraphPad Prism software version 7 (www.graphpad.com) and R version 3.6.1 software (www.r-project.org; ref. 25)

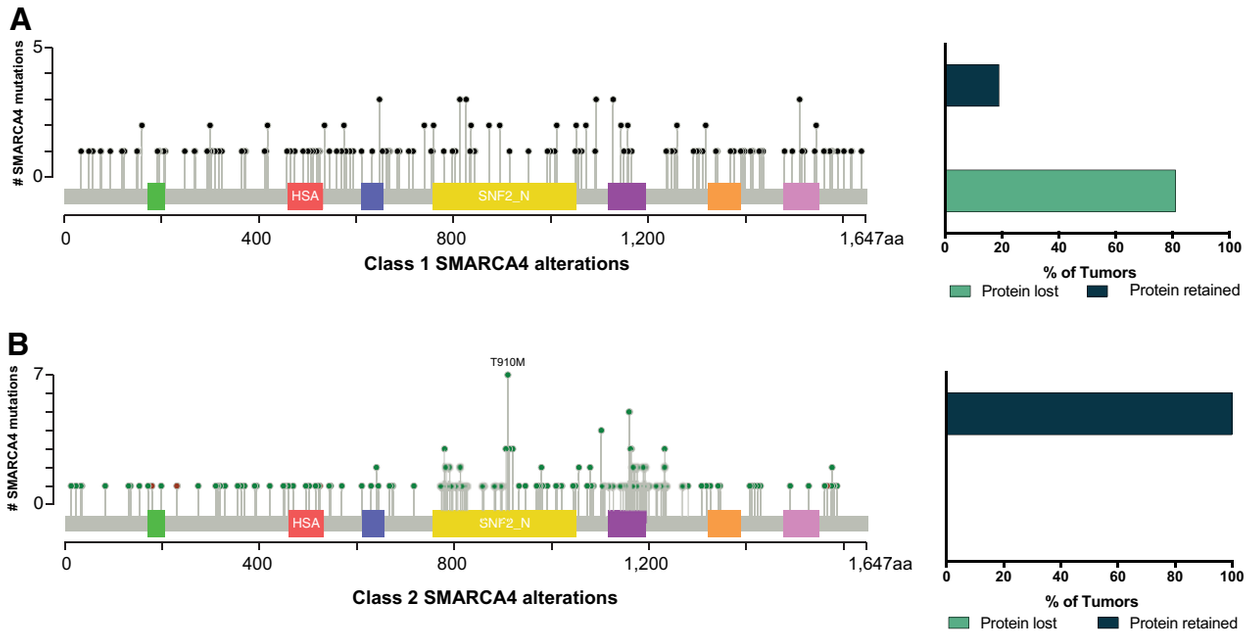


Figure 1.

Spectrum of *SMARCA4* alterations by class and association with SMARCA4 protein expression. **A,** The distribution of class 1 *SMARCA4* alterations ($n = 212$) and protein expression ($n = 62$). **B,** The distribution of class 2 *SMARCA4* alterations ($n = 95$) and protein expression ($n = 24$). Green QLQ, Gln, Leu, Gln motif; Red HSA, helicase/SANT-associated domain; Blue BRK, Brahma and Kismet domain; Yellow DEXDc, DEAD-like helicase superfamily domain; Purple SNF2_N, SNF2 family N-terminal domain; Orange HELICc, helicase superfamily C-terminal domain; Pink Bromo, bromodomain.

Results

Spectrum of *SMARCA4* genomic alterations

In patients with NSCLC tested by comprehensive next-generation sequencing, 8% ($n = 407$ of 4,813) had a *SMARCA4* alteration, with an array of *SMARCA4* alterations identified (**Fig. 1**). *SMARCA4* alterations were categorized into two groups based upon the type of genomic abnormality: (i) "class 1 alterations" included truncating mutations deemed oncogenic, gene fusions, and homozygous deletions and (ii) "class 2 alterations" included all missense mutations and other variants of unknown significance based upon categorization in OncoKB (23). Tumors with concurrent class 1 and class 2 *SMARCA4* alterations were categorized as class 1 tumors. In total, 212 patients (4% of total, 52% of *SMARCA4* variants) had tumors with class 1 *SMARCA4* alterations, and 195 (4% of total, 48% of *SMARCA4* variants) had tumors with class 2 *SMARCA4* alterations (**Fig. 1**).

Relationship between class of *SMARCA4* genomic alteration and protein expression

We next explored the relationship between the genomic class of *SMARCA4* alteration and protein expression. Sufficient tissue for SMARCA4 IHC analysis was available for 86 cases, including 62 tumors with class 1 (truncating) alterations and 24 tumors with class 2 (missense) alterations. SMARCA4 expression loss was identified in 50 cases, all of which were tumors with class 1 alterations (81% of class 1 alterations). Overall, loss of SMARCA4 expression was significantly associated with class 1 alterations ($P < 0.001$; **Fig. 1**).

Molecular landscape associated with *SMARCA4* alterations

To evaluate the genomic context of *SMARCA4* alterations, we evaluated genomic profiles of tumors harboring *SMARCA4* alterations ($n = 407$) and those without *SMARCA4* alterations ($n = 4{,}406$). Among commonly altered genes in lung cancer, the most frequent co-occurring mutations with *SMARCA4* alterations were *TP53* (56%), *KEAP1* (41%), *STK11* (39%), and *KRAS* (36%; **Fig. 2A** and **B**).

We identified multiple genes that were associated with *SMARCA4* alterations (**Fig. 2C**). Mutations in *STK11* and *KEAP1* had the strongest association with *SMARCA4*-mutant tumors compared with *SMARCA4* wild-type tumors ($P < 0.001$, $q < 0.001$; $P < 0.001$, $q < 0.001$; **Fig. 2B** and **C**). Conversely, *EGFR* alterations were strongly associated within *SMARCA4* wild-type tumors compared with *SMARCA4* mutants ($P < 0.001$, $q < 0.001$). *SMARCA4* alterations occurred in the absence of *KRAS, STK11*, and *KEAP1* alterations in 38% of cases (**Fig. 2D**). *STK11* alterations occurred significantly more frequently with class 1 than class 2 alterations ($P < 0.001$, $q = 0.08$, Supplementary Table S1). *NKX2-1* and *KEAP1* alterations also occurred more frequently with class 1 alterations ($P = 0.002$, $q = 0.19$; $P = 0.01$, $q = 0.34$ respectively), and *EGFR* alterations were common with class 2 alterations ($P = 0.004$, $q = 0.19$, Supplementary Table S1).

Patient characteristics in advanced NSCLC by *SMARCA4* alteration class

We then investigated how the findings from our molecular and expression analyses related to clinical outcomes in patients with advanced NSCLC. Patient characteristics among stage IV tumors with class 1 ($n = 149$) versus class 2 ($n = 143$) *SMARCA4* alterations were generally similar (**Table 1**). The presence of a class 1 or 2 *SMARCA4* alteration was associated with history of smoking ($P < 0.001$) and nonadenocarcinoma histology ($P < 0.001$) compared with patients with *SMARCA4* wild-type NSCLC ($n = 996$; **Table 1**). Among patients

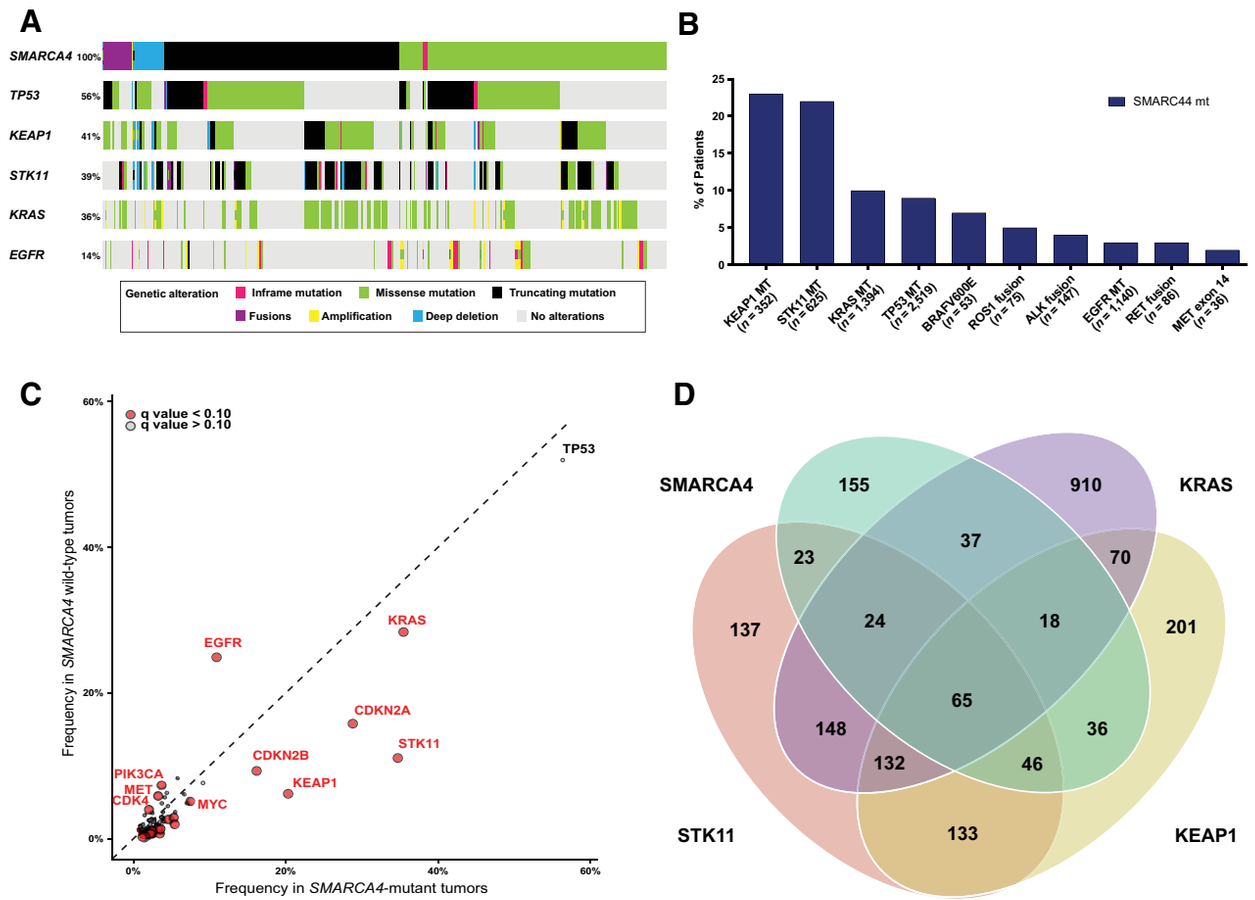


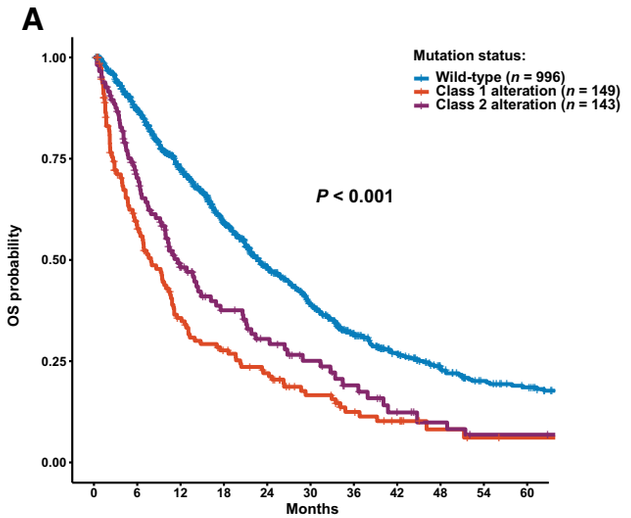
Figure 2.

Genomic context of *SMARCA4* alterations. **A,** Most frequent co-occurring alterations by *SMARCA4* alteration. **B,** Distribution of *SMARCA4* alteration by commonly altered gene subgroups in NSCLC. **C,** Frequency of altered individual genes within *SMARCA4* mutant versus *SMARCA4* wild-type subgroups. Genes labeled red were associated with significantly differential PD-L1 expression (*q* value < 0.10). **D,** Distribution of *SMARCA4, STK11, KRAS*, and *KEAP1* alterations within NSCLC cohort.

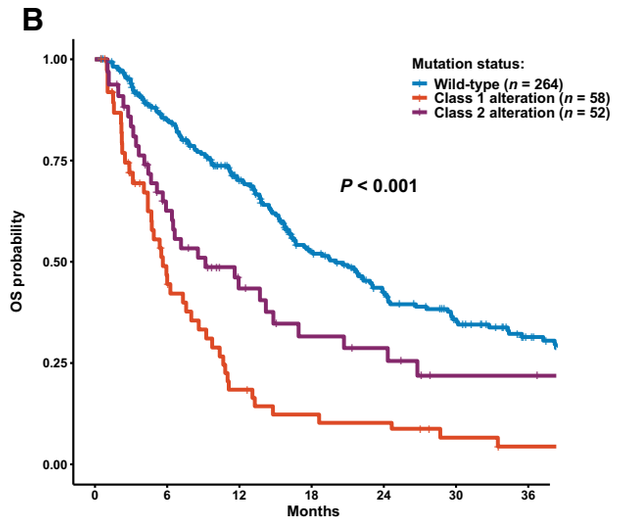
Table 1. Clinical characteristics of patients with advanced NSCLC by *SMARCA4* alteration class.

Characteristic	*SMARCA4* Class 1 (*N* = 149)	*SMARCA4* Class 2 (*N* = 143)	*SMARCA4* Wild-type (*N* = 996)	*P* value
Median age (Q1, Q3)	65 (58, 72)	65 (59, 72)	65 (58, 73)	0.7
Sex				0.052
Female	74 (50%)	78 (55%)	593 (60%)	
Male	75 (50%)	65 (45%)	403 (40%)	
Race				0.13
White	124 (83%)	125 (87%)	775 (78%)	
Black	7 (5%)	7 (5%)	57 (6%)	
Asian	10 (7%)	6 (4%)	101 (10%)	
Other	8 (5%)	5 (4%)	63 (6%)	
Smoking				<0.001
Never smoker	17 (11%)	26 (18%)	315 (32%)	
Former light (<15 py)	20 (13%)	19 (13%)	165 (17%)	
Former heavy (>15 py)	80 (54%)	71 (50%)	373 (37%)	
Current smoker	32 (21%)	27 (19%)	131 (13%)	
Histology				<0.001
Adenocarcinoma	121 (81%)	125 (87%)	914 (92%)	
Other	28 (19%)	18 (13%)	82 (8%)	

Abbreviation: py, pack years.



N = 1,288	HR	95% CI	*P* value
SMARCA4 mutation type			<0.001
Wild-type	--	--	
Class 2	2.01	1.58–2.55	
Class 1	1.59	1.25–2.04	
Sex			0.2
Female	--	--	
Male	1.12	0.95–1.31	
Age (10 years)	1.22	1.13–1.32	<0.001
Smoking status			0.005
Never smoker	--	--	
Former light (<15 pack-year)	1.58	1.23–2.03	
Former heavy (>15 pack year)	1.21	0.96–1.51	
Current smoker	1.27	0.96–1.69	
Histology			<0.001
Adenocarcinoma	--	--	
Nonadenocarcinoma	1.79	1.38–2.33	
Tumor mutation burden (TMB)	0.98	0.97–0.99	<0.001
STK11			<0.001
Negative	--	--	
Positive	1.52	1.23–1.88	
KEAP1			0.036
Negative	--	--	
Positive	1.26	1.02–1.55	



N = 374	HR	95% CI	*P* value
SMARCA4 mutation type			<0.001
Wild-type	--	--	
Class 2	2.75	1.84–4.11	
Class 1	1.59	1.04–2.41	
Sex			0.6
Female	--	--	
Male	0.93	0.70–1.25	
Age (10 years)	1.33	1.13–1.55	<0.001
Smoking status			0.7
Never smoker	--	--	
Former light (<15 pack-year)	1.03	0.49–2.16	
Former heavy (>15 pack year)	1.12	0.59–2.14	
Current smoker	0.88	0.43–1.78	
Histology			0.13
Adenocarcinoma	--	--	
Nonadenocarcinoma	1.61	0.90–2.90	
Tumor mutation burden (TMB)	0.97	0.95–1.00	0.023
STK11			0.017
Negative	--	--	
Positive	1.51	1.08–2.11	
KEAP1			0.10
Negative	--	--	
Positive	1.34	0.95–1.89	

Figure 3.
Survival by *SMARCA4* alteration class. **A,** OS among all patients, with multivariate model (right). **B,** OS among patients with *KRAS* mutations, with multivariate model (right).

harboring either class of *SMARCA4* mutation, 85% were smokers and 84% had adenocarcinoma; the rest had predominantly NSCLC, not otherwise classified.

Prognostic impact of class 1 and class 2 *SMARCA4* alterations in advanced NSCLC

Overall, we found that patients with metastatic NSCLC harboring either class 1 or class 2 *SMARCA4* alterations had shorter OS compared with patients with *SMARCA4* wild-type NSCLC ($P <$ 0.001; **Fig. 3A**). class 1 alterations were associated with the poorest outcomes (**Fig. 3A**). The differences in outcomes held in the multivariable survival analysis adjusted for age, sex, smoking status, histology, TMB, and the presence of *STK11* and/or *KEAP1* mutations (**Fig. 3A**).

Given the heterogeneity of co-occurring mutations, we sought to further isolate the specific impact of *SMARCA4* alterations by examining within the context of a single driver oncogene. We focused initially on 374 patients with tumors harboring *KRAS* mutations. In these patients, the presence of class 1 or class 2 *SMARCA4* alterations was a poor prognostic factor and remained prognostic when accounting for age, sex, smoking status, histology, TMB, and the presence of *STK11* or *KEAP1* mutations (**Fig. 3B**). Further, the addition of *STK11* and/or *KEAP1* was associated with decreased survival, with patients with all three *STK11, KEAP1*, and *SMARCA4* having the shortest survival ($P < 0.001$, Supplementary **Fig. S2**).

Association with benefit of immunotherapy

Next, we analyzed the impact of ICIs on patient outcomes. Among patients with *SMARCA4* alterations, ICI use was associated with significantly improved survival from the start of ICIs (HR, 0.67; 95% CI, 0.48–0.92; $P = 0.01$; **Fig. 4A**). When evaluating known factors that predict outcomes to ICI, *SMARCA4*-mutant tumors had higher TMB ($P < 0.001$, **Fig. 4B**) but were more likely to be PD-L1 low or negative ($P = 0.03$, **Fig. 4C**). class 1 alterations had lower expression of

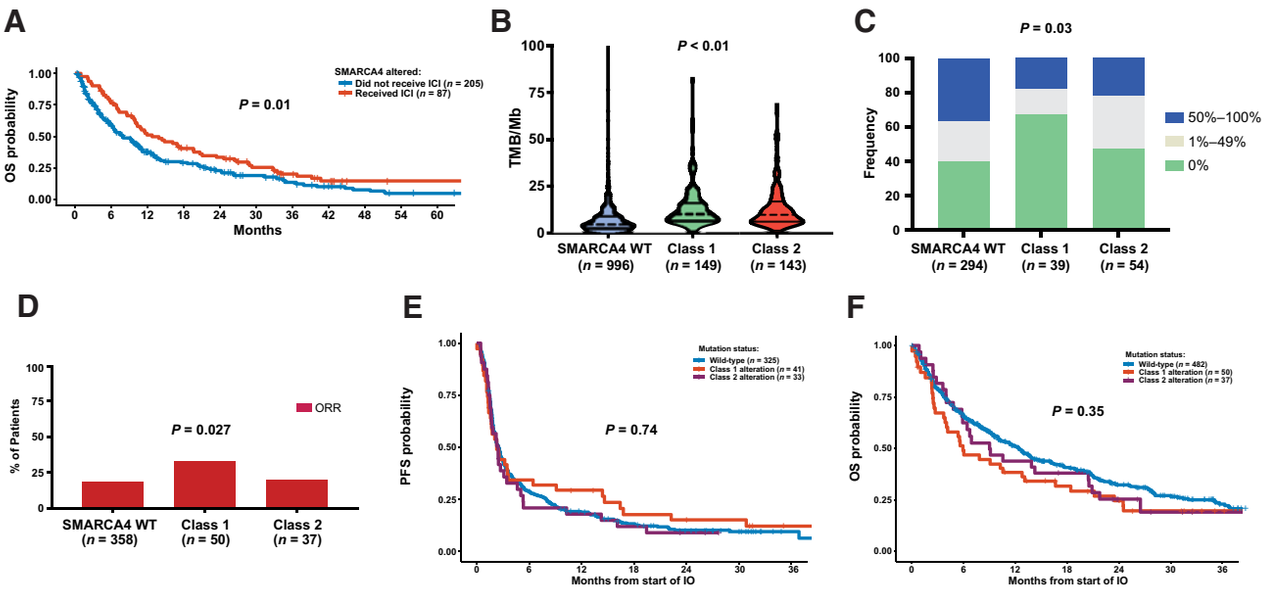


Figure 4.

PD-L1 expression, TMB, and ICI outcomes. **A,** OS among patients with *SMARCA4* alterations who did and did not receive ICIs. **B,** TMB by *SMARCA4* alteration class. **C,** PD-L1 expression frequency by *SMARCA4* alteration class. **D,** ORR by *SMARCA4* alteration class. **E,** PFS by *SMARCA4* alteration class. **F,** OS by *SMARCA4* alteration class.

PD-L1 and higher median TMB compared with class 2 alterations (**Fig. 4B–C**).

Finally, we sought to compare outcome among the two *SMARCA4*-mutant classes and *SMARCA4* wild-type NSCLC in patients who had received ICI. Overall response was assessed in 445 out of 570 patients that received ICI. In unadjusted analyses, patients who harbored class 1 alterations had a higher ORR in comparison with class 2 alterations or *SMARCA4* wild-type tumors ($P = 0.027$, **Fig. 4D**). There was no difference in PFS ($P = 0.74$) or OS ($P = 0.35$) on ICIs by *SMARCA4* alteration status (**Fig. 4E–F**).

Discussion

Here, we identify two specific classes of *SMARCA4* alterations associated with distinct protein expression and differential negative clinical outcomes in patients with metastatic NSCLC. Although both classes of *SMARCA4* alterations are associated with poor clinical outcomes, class 1 alterations, which are associated with protein loss, are the strongest independent negative prognostic factor for patients, but respond best to ICIs. Despite the negative prognostic impact compared with patients with *SMARCA4* wild-type tumors, patients with *SMARCA4* alterations who received ICIs had better outcomes than those who did not.

This study builds upon recent data that co-occurring *STK11* and *KEAP1* mutations in lung cancer can significantly impact prognosis and responsiveness to therapy. *STK11* and *KEAP1* alterations are linked with poor prognosis and lack of response to immunotherapy in *KRAS*-mutant tumors and more recently in all patients with NSCLC. We find that *SMARCA4* alterations are associated with *STK11* and *KEAP1* mutations but are independent predictors of poor prognosis. *SMARCA4* abnormalities in combination with *STK11* and/or *KEAP1* mutations have an additive impact on shortening survival. However, unlike *STK11, SMARCA4* appears to be associated with increased sensitivity to immunotherapy. Future studies of *STK11* and *KEAP1* should incorporate exploration of *SMARCA4* to further delineate the role of each co-occurring mutation in influencing patient outcomes, and *SMARCA4* should be identified and tested as a potential prognostic or predictive variable in prospective trials moving forward.

We observed that the spectrum of *SMARCA4* alterations differentially affects protein expression. Our findings are consistent with other recent analyses that assessed the incidence of *SMARCA4*-mutant lung cancer and frequency of protein expression loss with truncating mutations, supporting our classification schema (8, 10). Interestingly, although the effect of class 1 (truncating) alterations was most profound, we also find that, unexpectedly, patients with class 2 (mis-sense, nontruncating) *SMARCA4* alterations had worse overall prognosis relative to patients with *SMARCA4* wild-type tumors, suggesting that function may be compromised in the setting of intact expression. Recent preclinical work provides additional mechanistic support and reveals that missense mutations of *SMARCA4* modify the open chromatin landscape and induce pro-oncogenic expression changes in MYC and its target genes, among others (26, 27).

Our study is the first to evaluate how *SMARCA4* alterations in NSCLC influence sensitivity to ICIs. Recent analyses have shown that *SMARCA4* and *PBRM1* could be associated with improved response to immunotherapy in subtypes of ovarian cancer and renal cell cancer (4, 19), and case reports have described durable responses to ICIs in a patient with a thoracic *SMARCA4*-deficient undifferentiated tumor (also referred to as a *SMARCA4*-deficient thoracic sarcoma) and a patient with NSCLC (20, 21). Despite high rates of PD-L1 negativity, patients with *SMARCA4*-mutant NSCLC appear to derive significant benefit from PD-(L)1 blockade. Therefore, *SMARCA4* mutation status should be explored as a potentially novel biomarker of responsiveness to ICIs as a complement to PD-L1 expression and TMB in NSCLC.

Although there are no known currently effective targeted treatments for *SMARCA4*-mutant NSCLCs, our study and others suggest *SMARCA4* is a potential target in lung cancer with distinct therapeutic vulnerabilities. For example, CDK4/6, AURKA, ATR, and EZH2 inhibition have recently shown antitumor activity in preclinical models of *SMARCA4*-deficient tumors (1, 16, 25, 28–33). *SMARCA2* could be a synthetic lethal vulnerability in *SMARCA4*-mutant cancers. Prior reports have shown that SMARCA2 retains expression in *SMARCA4*-mutant NSCLC, and several SMARCA2 inhibitors are currently in development to target this potential vulnerability (10, 16). Future trials should explore use of these agents alone or in combination with ICIs given the efficacy of anti–PD-(L)1 antibodies in our analysis.

This study is a single-institution retrospective analysis and therefore has some inherent limitations. Unidentified factors associated with exposure and response to immunotherapy and OS could bias our results. Nevertheless, we accounted for all known potential variables that may influence outcomes. For example, we developed and incorporated a risk score to account for a patient's likelihood of receiving anti–PD-(L)1 therapy and used a Cox proportional hazards model for multivariate analysis using the variables available. Analyses adjusting for PD-L1 expression are limited by the modest number of patients with sufficient available tissue for retrospective staining for PD-L1 and SMARCA4. Future studies that incorporate zygosity are also needed to understand its impact on expression and clinical outcomes.

In sum, our report highlights that *SMARCA4* alterations in lung cancer are uniquely linked to response to immunotherapy and patient outcomes. We found that the presence of *SMARCA4* abnormalities is enriched in patients with *KRAS, STK11*, and *KEAP1* mutations, but independently contributes to shortened OS with these co-occurring alterations. Despite these poor outcomes, patients with *SMARCA4*-mutant lung cancers may also be more sensitive to immunotherapy, which may enable new therapeutic options in the future.

Disclosure of Potential Conflicts of Interest

J.A. Lavery reports other from American Association for Cancer Research (Salary support) outside the submitted work. C.P. Concepcion reports other from American Cancer Society (Postdoctoral Fellowship) and other from Koch Institute (Quinquennial Postdoctoral Fellowship) during the conduct of the study. M.E. Arcila reports other from InVivoscribe (speaker fees) and other from Biocartis (speaker fees) outside the submitted work. T. Jacks is a member of the Board of Directors of Amgen and Thermo Fisher Scientific, is a co-Founder of Dragonfly Therapeutics and T2 Biosystems, and serves on the Scientific Advisory Board of Dragonfly Therapeutics, SQZ Biotech, and Skyhawk Therapeutics; none of these affiliations represent a conflict of interest with respect to the design or execution of this study or interpretation of data presented in this manuscript. T. Jacks laboratory currently also receives funding from the Johnson & Johnson Lung Cancer Initiative and The Lustgarten Foundation for Pancreatic Cancer Research, but this funding did not support the research described in this manuscript. C.M. Rudin reports personal fees from AbbVie, Amgen, Astra Zeneca, Bicycle, Celgene, Genentech/Roche, Ipsen, Jansen, Jazz, Lilly/Loxo, Pfizer, PharmaMar, Syros, Vavotek, Bridge Medicines (SAB), and Harpoon Therapeutics (SAB) outside the submitted work. B.S. Taylor reports grants and personal fees from Genentech, Inc., personal fees from Boehringer Ingelheim, and personal fees from Loxo Oncology at Lilly outside the submitted work. M.D. Hellmann reports grants, personal fees, and non-financial support from BMS, personal fees and non-financial support from AstraZeneca, Shattuck Labs, and Arcus, personal fees from Merck, Roche/Genentech, Nektar, Syndax, Mirati, Immunai, Blueprint, and Achilles, and non-financial support from Eli Lilly during the conduct of the study, and reports a patent for PCT/US2015/062208 pending and licensed to PGDx. G.J. Riely reports grants from NCI during the conduct of the study; grants and other from Pfizer (institutional grant and editorial costs associated with publications of sponsored research), Novartis (institutional grant and editorial costs associated with publications of sponsored research), Takeda (institutional grant and editorial costs associated with publications of sponsored research), and grants from Merck and Roche outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

A.J. Schoenfeld: Conceptualization, supervision, investigation, writing-original draft, writing-review and editing. **C. Bandlamudi:** Data curation, formal analysis, methodology, writing-review and editing. **J.A. Lavery:** Data curation, software, formal analysis, methodology, writing-original draft, writing-review and editing. **J. Montecalvo:** Formal analysis, methodology, writing-review and editing. **A. Namakydoust:** Conceptualization, supervision, writing-review and editing. **H. Rizvi:** Data curation, formal analysis, investigation, methodology, writing-review and editing. **J. Egger:** Data curation, project administration, writing-review and editing. **C.P. Concepcion:** Supervision, investigation, writing-review and editing. **S. Paul:** Data curation, writing-review and editing. **M.E. Arcila:** Resources, validation, investigation, writing-review and editing. **Y. Daneshbod:** Investigation, methodology, writing-review and editing. **J. Chang:** Resources, supervision, investigation, methodology, writing-review and editing. **J.L. Sauter:** Resources, investigation, methodology, writing-review and editing. **A. Beras:** Data curation, project administration, writing-review and editing. **M. Ladanyi:** Resources, supervision, investigation, methodology, writing-review and editing. **T. Jacks:** Conceptualization, supervision, writing-review and editing. **C.M. Rudin:** Conceptualization, resources, supervision, validation, writing-review and editing. **B.S. Taylor:** Resources, supervision, writing-review and editing. **M.T.A. Donoghue:** Resources, supervision, methodology, writing-review and editing. **G. Heller:** Conceptualization, formal analysis, supervision, validation, investigation, methodology, writing-review and editing. **M.D. Hellmann:** Conceptualization, supervision, writing-review and editing. **N. Rekhtman:** Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **G.J. Riely:** Conceptualization, resources, formal analysis, supervision, validation, investigation, visualization, methodology, writing-review and editing.

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