ORIGINAL ARTICLE

Clinicopathologic Characteristics and Outcomes for Patients With *KRAS* G12D-Mutant NSCLC

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ABSTRACT

Introduction: Co-occurring mutations in *KRAS*-mutant NSCLC are associated with discrete biological properties and modulate therapeutic susceptibilities. As G12D-specific inhibitors are expected to enter the clinic, we sought to investigate the characteristics and outcomes of patients with *KRAS* G12D-mutant NSCLC.

Methods: This was a retrospective single-institution study. Patients with NSCLC and *KRAS* G12D mutations detected by the Massachusetts General Hospital SNaPshot next-generation sequencing assay were identified. Clinical and pathologic characteristics were collected by chart review.

Results: A total of 107 patients with *KRAS* G12D-mutant NSCLC were identified. Most patients were former smokers (80, 74.8%) and had tumors with adenocarcinoma pathologic subtype (93, 86.9%). Among 56 patients evaluated for programmed death-ligand 1 expression, tumor proportion score was less than 50% in 43 (76.8%). Concomitant mutations were identified in *STK11* (17 of 107, 15.9%), *KEAP1* (10 of 58, 17.2%), *TP53* (36 of 107, 33.6%), and *SMARCA4* (11 of 107, 10.3%). Among 57 patients treated with first-line therapy, patients with *STK11* co-mutations had shorter progression-free survival (1.2 mo, 95% confidence interval [CI]: 0.6–2.9 versus 4.1 mo, 95% CI: 2.5–6.0, $p = 0.0235$) and overall survival (4.3 mo, 95%

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CI: 1.2–10.6 versus 17.9 mo, 95% CI: 8.6–31.1, $p = 0.0018$) compared with wild type. Patients with *KEAP1* co-mutations had shorter overall survival (4.6 mo, 95% CI: 1.2–10.6 versus 17.9 mo, 95% CI: 7.1–30.1, $p = 0.0125$) than those without. *TP53* co-mutations exerted no influence on survival.

Conclusions: Co-occurring mutations were common in patients with *KRAS* G12D-mutant NSCLC. *STK11* and *KEAP1* co-mutations were associated with worse clinical outcomes, whereas co-occurring *TP53* did not affect survival.

Keywords: Non–small cell lung cancer; *KRAS* mutation; Targeted therapies; Co-mutations

Introduction

The ability to identify and therapeutically target oncogenic driver alterations is a cornerstone of the current treatment paradigm for NSCLC.[1,2] Mutations in the *KRAS* gene are among the most often identified oncogenic drivers in patients with NSCLC,[3] with G12C, G12V, and G12D representing the most frequently occurring mutations.[4] RAS-mediated pathways regulate signaling cascades involved in cell proliferation and survival.[4] *KRAS* missense mutations drive constitutive activation of the RAS protein and promote cancer cell growth and survival.[5]

KRAS G12D inhibitors are currently have promising efficacy in preclinical studies[6] and are expected to soon enter clinical trials. This article aims to describe the clinicopathologic characteristics of *KRAS* G12D lung cancer and outcomes within this population by co-mutation status. Though recent work has compared outcomes for patients across *KRAS* mutation subtypes,[7–11] or in comparison with *KRAS* wild-type NSCLC,[12] relatively little is known about the specific characteristics and outcomes for patients with *KRAS* G12D-mutant NSCLC. This is a considerable gap in the literature, and an understanding of how patients with G12D lung cancer fared before the advent of G12D-specific inhibitors will be needed. Previous literature has revealed an association with never or minimal smoking status,[13–16] including the potential for a poor prognosis compared with other *KRAS* mutation subtypes.[11,17] The co-mutational profile, which has emerged as a considerable modulator of prognostic and predictive effect in *KRAS*-mutated NSCLC, is of particular interest, as co-occurring alterations such as *STK11/LKB1*, *KEAP1*, *TP53*, and *SMARCA4* have been associated with discrete biological properties and therapeutic susceptibilities in *KRAS*-mutant lung cancer.[18–20] In anticipation of cohorts of patients with *KRAS* G12D-mutant NSCLC soon to be treated with targeted inhibitors, we aimed to investigate the clinical characteristics and outcomes of these patients with particular attention to associated co-mutational profile.

Materials and Methods

Patients

We conducted a retrospective study to evaluate the clinicopathologic characteristics and clinical outcomes of patients with NSCLC harboring *KRAS* G12D. Patients with NSCLC at the Massachusetts General Hospital (MGH) undergo tumor genotyping using the SNaPshot next-generation sequencing assay. This test uses anchored multiplex polymerase chain reaction technology on DNA and RNA for calling of single-nucleotide variants, insertions, deletions, copy number changes, and fusion transcripts.[21] We identified patients whose SNaPshot testing results revealed *KRAS* G12D mutation by systematically querying the molecular database. We excluded one patient with a concomitant sensitizing *EGFR* mutation. We conducted chart review to evaluate clinical, demographic, and pathologic characteristics including co-mutation status. Programmed death-ligand 1 (PD-L1) immunohistochemistry was performed using the clone E1L3N (Cell Signaling Technology) in all cases except one, in which testing was done at an outside institution and antibody clone could not be verified. PD-L1 expression was assessed by means of tumor proportion score. Treatment history was obtained by review of clinical notes. Co-occurring molecular alterations were classified within pathways by searching for each alteration's pathway in cBioPortal for Cancer Genomics.[22] The study was performed in accordance with an MGH institutional review board-approved protocol.

Treatment Outcomes

Progression-free survival (PFS) was calculated for patients with metastatic disease from time of treatment initiation to date of progression, death, or last known date without progression, with progression defined by the treating physician's assessment. Overall survival (OS) was calculated for patients with metastatic disease from time of treatment initiation for metastatic disease to date of death or last known date alive. Time-to-event analysis (PFS and OS) was performed with the Kaplan-Meier method. The log-rank test was used for the comparison between survival curves. SAS 4.0 was used for all statistical analyses. We stratified survival analyses by the

status of co-mutations in *STK11*, *KEAP1*, *TP53*, and *SMARCA4* given previous data revealing differential outcomes in patients with these co-mutational profiles.[18–20]

Results

Clinical, Pathologic, and Molecular Characteristics

Among all patients at MGH who underwent SNaPshot testing between May 2014 and August 2021, 665 had cancers with *KRAS* G12D mutations, including 107 patients with NSCLC (16.1%) (Supplementary Fig. 1). Clinical, demographic, histologic, and molecular characteristics of patients with NSCLC are summarized in Table 1. Median age was 68 (range: 29–90) years, and 59.8% were of female sex. Most patients were former smokers (80, 74.8%) with median pack-years of 25. Many patients presented with stage IV disease at initial diagnosis (51, 47.7%), and another 24 patients eventually developed metastatic disease for a total of 75 (70.1%). Furthermore, 27 of 75 patients had central nervous system metastases at any time. Histology for most patients was adenocarcinoma (93, 86.9%). Analysis of co-mutation status revealed that 17 patients (15.9%) had co-occurring *STK11* mutations and 36 patients (33.6%) had *TP53* mutations. Among 58 patients with KEAP1 testing, 10 (17.2%) were positive. Co-occurrence of these mutations was uncommon (Table 1). Other notable mutations are displayed in Figure 1 and are listed in detail in Supplementary Table 1. In brief, 20 patients had co-occurring mutations in the RTK/RAS/MAPK pathway (18.7%), 12 in the PI3K/AKT/mTOR pathway (11.2%), 17 in cell-cycle–related genes (15.9%), 11 in the WNT pathway (10.3%), 11 in *SMARCA4* (10.3%), two in *SMARCB1* (1.9%), and four in *ARID1A* (3.7%). Of the 51 patients whose NSCLC samples had mutations in *STK11*, *KEAP1*, and *TP53*, 35 had at least one other mutation. PD-L1 level was assessed in 56 patients; PD-L1 level was less than 1% in 24 patients (22.4%), 1% to 49% in 19 patients (17.8%), and greater than or equal to 50% in 13 patients (12.2%). Figure 2 illustrates a scattergram of PD-L1 expression by co-mutation. PD-L1 expression was similar among wild-type and mutant for *TP53* and *SMARCA4* mutations, but relatively lower in *STK11*- and *KEAP1*-mutant samples compared with wild type. Variant allele frequencies for *KRAS* G12D for each patient's tumor samples are enumerated in Supplementary Table 2.

Treatment Characteristics of Patients With Metastases

Of the 75 patients who had metastatic disease, 57 were treated with frontline systemic therapy; this

Table 1. Characteristics of Patients With *KRAS* G12D-Mutant NSCLC

Characteristics	Overall (N = 107)
Age at diagnosis, median (range)	68 (29-90)
Sex	
Male	43 (40.2)
Female	64 (59.8)
Race	
White	93 (86.9)
Black	3 (2.8)
Asian	3 (2.8)
Hispanic	4 (3.7)
Unavailable	4 (3.7)
Smoking status	
Never	17 (15.9)
Former	80 (74.8)
Current	10 (9.4)
Pack-years, median (range)	25 (0-150)
Initial stage	
Stage I	27 (25.2)
Stage II	8 (7.5)
Stage III	21 (19.6)
Stage IV	51 (47.7)
Ever metastatic	75 (70.1)
CNS mets	27 (36.0)
At initial diagnosis	14 (18.7)
Extrathoracic mets	51 (68.0)
At initial diagnosis	37 (49.3)
Histology	
Adenocarcinoma	93 (86.9)
Squamous cell	2 (1.9)
Adenosquamous	1 (0.9)
Other	11 (10.3)
PD-L1	
<1%	24 (22.4)
1%-49%	19 (17.8)
≥50%	13 (12.2)
Not evaluated	51 (47.7)
Co-mutation present	
STK11	17 (15.9)
KEAP1[a]	10 (9.4)
TP53	36 (33.6)
STK11/KEAP1	7 (6.5)
STK11/TP53	3 (2.8)
KEAP1/TP53	2 (1.9)
STK11/KEAP1/TP53	1 (0.9)
	Metastatic (n = 57)
First-line systemic treatment received	
Chemotherapy alone	29 (50.9)
Platinum + pemetrexed	19 (33.3)
Platinum + taxane	2 (3.5)
Pemetrexed alone	3 (5.3)
Included VEGF inhibitor	5 (8.8)
Immunotherapy alone	17 (29.8)
Pembrolizumab	13 (22.8)
Atezolizumab	1 (1.8)
Nivolumab	1 (1.8)
Ipilimumab + nivolumab	2 (3.5)
Chemotherapy + immunotherapy	11 (19.3)

(continued)

Table 1. Continued

Characteristics	Overall (N = 107)
Treatment lines	
One	24 (42.1)
Two	22 (38.6)
Three	4 (7.0)
Four or more	7 (12.3)

CNS, central nervous system; mets, metastases; PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor.
[a]KEAP1 not evaluated in 49 patients (45.8%) with an earlier version of SNaPshot performed. Among 58 patients with KEAP1 testing, 10 (17.2%) were positive.

consisted chemotherapy (chemo) alone in 29 patients (50.9%), immunotherapy (IO) alone in 17 (29.8%), and combination chemo and IO (chemo/IO) in 11 (19.3%). Most patients received one (24, 42.1%) or two (22, 38.6%) lines of therapy (range: 1–7) (Table 1; Supplementary Figure 2). Treatment type by co-mutation status is displayed in Table 2. In our cohort, approximately half of the patients with each co-mutation were treated with chemo alone, with the remaining patients receiving an IO-containing regimen (IO alone or chemo-IO).

First-line treatment was terminated for progression in 38 cases (66.7%) and for toxicity in eight cases (14%). Other reasons for termination were identified in five cases (8.8%), including two (3.5%) in which treatment was stopped owing to stable disease after two years of therapy. Information regarding reason for treatment termination was missing in three cases (5.3%), and treatment was ongoing at the time of this analysis for three patients (5.3%).

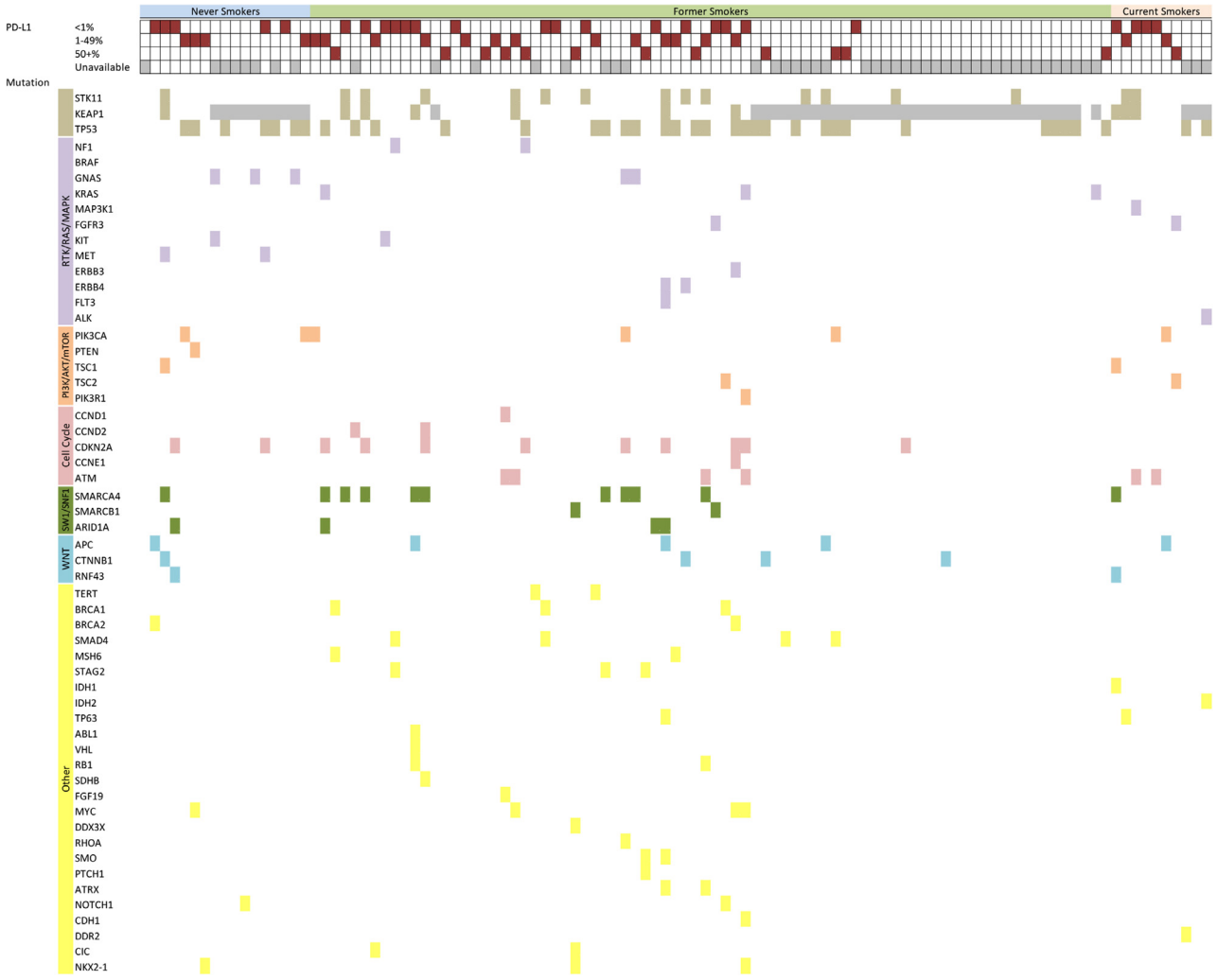

Figure 1. Summary of PD-L1 level and molecular alterations in patients with *KRAS* G12D-mutated NSCLC. This heatmap summarizes the findings of PD-L1 level (top) and molecular alterations (bottom) for each patient in the cohort, with never smokers (blue), former smokers (green), and current smokers (peach) delineated. Squares populated with gray in the PD-L1 and KEAP1 fields indicate that these tests, respectively, were not available for inclusion. PD-L1, programmed death-ligand 1.

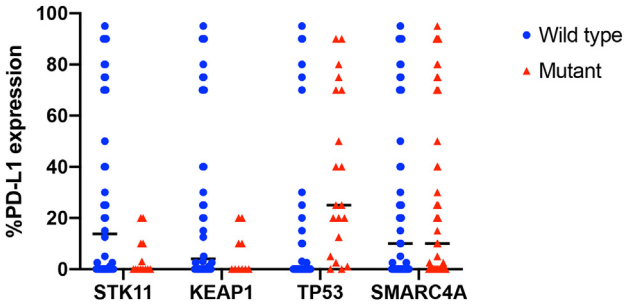

Figure 2. Association of PD-L1 level with molecular alterations. Scatterplot of percent expression of PD-L1 (y axis) is illustrated in relationship to molecular wild-type (blue circles) or mutant (red triangles) status. PD-L1 expression was similar among wild-type and mutant for *TP53* and *SMARCA4* mutations, but relatively lower in *STK11*- and *KEAP1*-mutant samples compared with wild type. PD-L1, programmed death-ligand 1.

Progression-Free Survival

Median PFS among patients with metastatic disease treated with first-line therapy was 3.0 months (95% confidence interval [CI]: 2.1–5.1) with a median follow-up time of 2.84 months (Fig. 3*A*). Analysis by co-occurring mutational status suggested that *STK11* and *SMARCA4* mutations were associated with shorter PFS, whereas *TP53* mutations had no effect. Median PFS for patients with co-occurring *STK11* mutations (n = 10) was 1.2 months (95% CI: 0.6–2.9) compared with 4.1 months (95% CI: 2.5–6.0) for *STK11* wild type (n = 47) ($p = 0.0235$) (Fig. 3*B*). Patients with *SMARCA4* mutations (n = 8) also had shorter PFS than patients who had *SMARCA4*-wild type disease (n = 49) (median PFS 1.5 mo [95% CI: 0.6–2.1] versus 4.0 mo [95% CI: 2.5–6.0], $p = 0.0039$) (Fig. 3*C*). Median PFS for patients with co-occurring *KEAP1* mutations (n = 7) was 2.1 months (95% CI: 0.6–no upper bound), compared with 2.8 months for *KEAP1* wild type (n = 32) (95% CI: 1.5–6.0, $p = 0.1087$, Fig. 3*D*). Median PFS for patients with co-occurring *TP53* mutations (n = 21) was not statistically different from *TP53* wild type (n = 36) (median PFS 4.7 mo [95% CI: 1.5–6.9] versus 2.8 mo [95% CI: 1.5–5.1], $p = 0.7253$) (Fig. 3*E*).

Overall Survival

Median OS in all 75 patients with metastatic disease was 11.9 (95% CI: 8.0–23.3) months with a median follow-up time of 10.64 months. Among the 57 patients treated with first-line systemic therapy, median OS was 10.6 (95% CI: 8.1–27.4) months (Fig. 4*A*). As observed in the PFS analyses, the presence of co-occurring *STK11* mutation was associated with worse outcomes, with median OS for patients with co-occurring *STK11* mutations of 4.3 months (n = 10) (95% CI: 1.2–10.6) compared with 17.9 months (95% CI: 8.6–31.1) in *STK11* wild type (n = 47, $p = 0.0018$, Fig. 4*B*). For patients with *KEAP1* mutations (n = 7), median OS was 4.6 months (95% CI: 1.2–10.6) compared with 17.9 months (95% CI: 7.1–30.1) in *KEAP1* wild type (n = 32, $p = 0.0125$, Fig. 4*D*). Although OS was numerically longer for wild-type patients, presence of *SMARCA4* or *TP53* mutations did not have a statistically significant effect on OS. Median OS was 6.1 (95% CI: 1.2–27.4) months for patients with co-occurring *SMARCA4* mutations (n = 8) versus 17.3 (95% CI: 8.6–29.1) months for patients with *SMARCA4* wild type (n = 49, $p = 0.4202$, Fig. 4*C*), and for patients with *TP53* mutations (n = 21), median OS was 10.6 (95% CI: 7.2–32.3) months compared with 17.3 (95% CI: 5.9–29.1) months for *TP53* wild type (n = 36, $p = 0.4175$, Fig. 4*E*).

Discussion

Here, we present detailed clinical, pathologic, and molecular characteristics and survival outcomes of patients with *KRAS* G12D-mutant NSCLC. In general, the clinical characteristics of our patient population were concordant with what has been previously described,

Table 2. First-Line Systemic Therapy Among Patients With Metastatic *KRAS* G12D-Mutant NSCLC by Presence or Absence of Co-Mutation

Co-Mutation	Chemotherapy Alone, n (%)	Immunotherapy Alone, n (%)	Chemoimmunotherapy, n (%)	Total n
STK11-mut	4 (40.0)	2 (20.0)	4 (40.0)	10
STK11-WT	25 (53.2)	15 (26.3)	7 (14.9)	47
KEAP1-mut	3 (42.9)	1 (14.3)	3 (42.9)	7
KEAP1-WT	13 (40.1)	11 (34.4)	8 (13.3)	32
KEAP1-unk	13 (72.2)	5 (27.8)	0 (0)	18
TP53-mut	12 (57.1)	9 (42.9)	0 (0)	21
TP53-WT	17 (47.2)	8 (22.2)	11 (30.1)	36
SMARCA4-mut	4 (50.0)	3 (37.5)	1 (12.5)	8
SMARCA4-WT	25 (51.0)	14 (28.6)	10 (20.4)	49

mut, mutated; unk, unknown; WT, wild type.

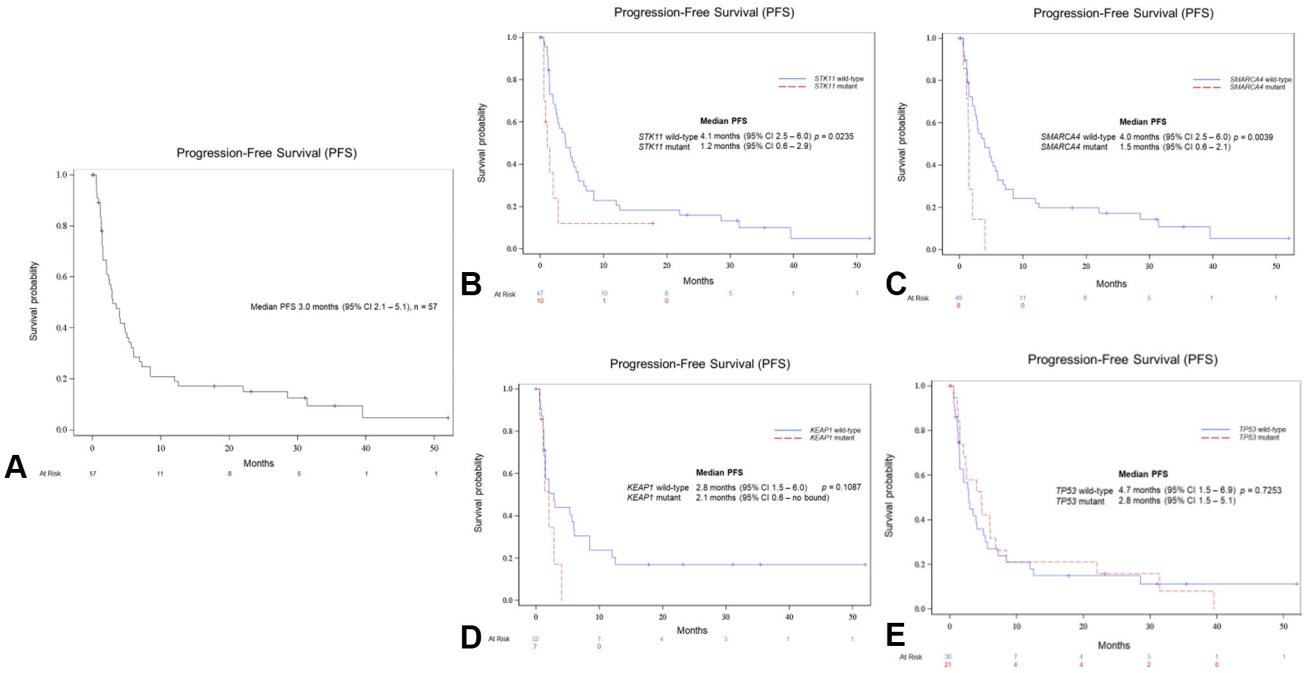

Figure 3. Median PFS among patients with metastatic disease treated with first-line therapy. PFS of the overall population is illustrated (*A*) and stratified by *STK11* mutation (*B*), *SMARCA4* mutation (*C*), *KEAP1* mutation (*D*), and *TP53* mutation (*E*). Plus signs represent data censored at the last time the patient was known to be without progression. CI, confidence interval; PFS, progression-free survival.

with one notable exception: in contrast to previous reports which identified *KRAS* G12D as more prevalent in never or minimal smokers,[9,10,13–16] our cohort had only 15.9% never smokers. The G12D amino acid change has not been associated with mutational signature traditionally associated with tobacco smoke,[23] so the predominance of ever smokers in our cohort is somewhat surprising, but it may indicate that the manifold

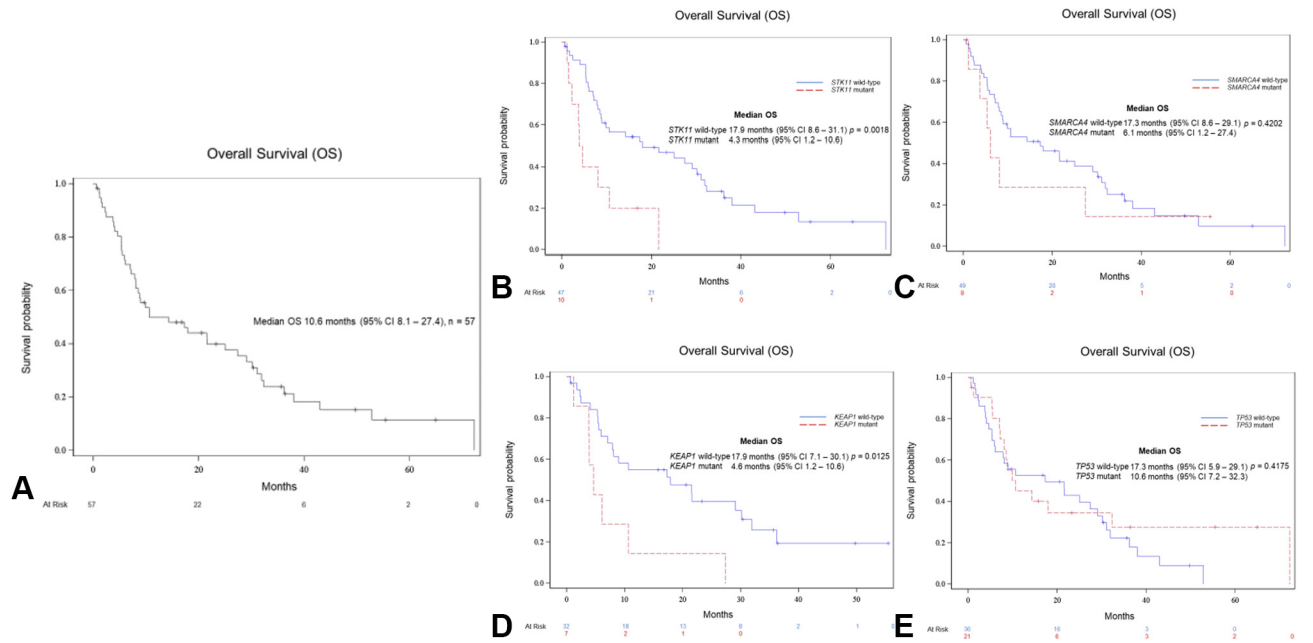

Figure 4. Median OS among patients with metastatic disease treated with first-line therapy. OS of the overall population is illustrated (*A*) and stratified by *STK11* mutation (*B*), *SMARCA4* mutation (*C*), *KEAP1* mutation (*D*), and *TP53* mutation (*E*). Plus signs represent data censored at the last time the patient was known to be alive. CI, confidence interval; OS, overall survival.

contributions to tumorigenesis do not hinge simply on the presence or absence of tobacco smoke as a carcinogen exposure. Nevertheless, the prevalence of co-occurring *STK11*, *KEAP1*, and *TP53* mutations in our data set is similar to what has been reported elsewhere,[11,24,25] suggesting our patient population, although small, is likely representative. In addition, the relatively low level of PD-L1 expression found in the *KRAS* G12D/*STK11*-mutated cohort recapitulates what has been revealed with other cohorts.[7,26,27]

Analysis with attention to co-mutational profile lends greater insight into patient outcomes in *KRAS* G12D NSCLC. We found that patients with *KRAS* G12D-mutant NSCLC with co-occurring *STK11* mutation had worse PFS and OS on first-line systemic treatment than *STK11* wild type, whereas *TP53* mutations exerted no influence. Patients with co-occurring *KEAP1* mutations had worse OS; a statistically significant difference in PFS was not found, although the numbers are small. Patients with *SMARCA4* mutations had poorer PFS, though this difference was not borne out in OS analyses. These results must be contextualized within what is currently known about co-mutations in both *KRAS*-mutant and *KRAS* wild-type NSCLC. Co-occurring alterations are key contributors to the tumor heterogeneity that is found in *KRAS*-mutated lung cancer, with alterations in *STK11*, *TP53*, and *KEAP1* defining distinct subtypes.[28]

A number of studies have revealed shorter survival times for patients with *STK11* mutations; some have indicated that the presence of this alteration may be prognostic without consideration of treatment history[11,14,24,29] and others have revealed poorer response to treatment.[12,30,31] Similarly, *KEAP1* mutations have been found to confer poorer outcomes both independent of[7] and related to treatment history[7,12,30,32] and in NSCLC without concurrent *KRAS* mutations.[33] As IO has emerged as the backbone of frontline treatment in NSCLC, special interest has developed in determining the impact of the co-mutational profile on treatment outcomes with immune checkpoint inhibitors. Inactivation of *STK11* in particular has been associated with a "cold" or barren immunologic tumor microenvironment, with paucity of tumor-infiltrating lymphocytes in both murine models and human tumor samples. This has led to the hypothesis that these co-mutations may render IO treatment less effective,[26] and indeed, several groups have revealed that co-mutations in *STK11*[26,27,34,35] and *KEAP1*[27] are associated with resistance to programmed cell death protein 1 blockade, worse PFS, and worse OS in *KRAS*-mutant lung cancer. Interestingly, when Ricciuti et al.[27] evaluated the effect of co-mutations among patients treated with first-line platinum chemo, they found that *STK11* and *KEAP1* mutations were associated with shorter PFS among *KRAS*-mutant lung cancer, but not wild type, in that setting as well. Our data are generally concordant with these results, though small sample size of the patients with *KEAP1*-mutant disease limited our ability to detect a statistically significant difference in PFS for this population.

In our data set, we did not have sufficient power to separate the first-line treatment by IO alone or chemo with IO. The findings of Ricciuti et al.[27] though, where *STK11* and *KEAP1* mutations were also noted to be associated with worse outcomes in the platinum-treated setting, suggest that the effect of these co-mutations might not be confined to the IO setting alone. Mutations in *STK11*, a tumor suppressor gene also known as *LKB1*, enable alterations in cell growth and polarity that facilitate tumorigenesis and promote metastasis[36,37] and decrease tolerance to oxidative stress.[38] The *KEAP1-NFE2L2* pathway regulates metabolic homeostasis[39] and oxidative damage response[40]; mutations in this pathway have been found to confer tumor survival advantage and promote an aggressive tumor subtype. Preclinical studies have revealed important differences in downstream signaling[41] and inflammatory microenvironment[18] on the basis of *STK11* and *TP53* status, including on metabolic programming on the basis of *STK11* and *KEAP1* mutations.[42,43] *KEAP1* mutations have been found to confer chemoresistance to NSCLC cells in both in vitro[44] and murine model experiments,[39] which may translate to a shorter duration of chemo in patients with *KEAP1*-mutated tumors.[25] Therefore, these alterations may affect clinical outcomes regardless of specific treatment type.

In contrast to the poorer outcomes found with traditional chemo or IO modalities, there has been a suggestion that targeted therapies may be especially beneficial for some co-mutant profiles. A preliminary exploratory analysis of patients with *KRAS* G12C treated with adagrasib in the KRYSTAL-1 study revealed that the objective response rate was higher in patients with co-mutations in *STK11*, though there were no differences in patients who harbored *KEAP1* or *TP53* co-mutations.[45] This effect was not replicated in the evaluation of response by co-mutation in studies of sotorasib, and indeed it seemed that there was a numerically lower response rate in patients with *KEAP1*-mutant cancer compared with wild type (20% versus 44%).[46] Although it is unknown whether such differences would also be found in patients with *KRAS* G12D treated with G12D-specific therapy, the differential survival outcomes found with standard first-line treatment suggest that these are indeed different populations with potentially different responses to therapy.

Interestingly, several groups have found that despite its significance as a co-mutation in other oncogene-driven tumor types,[47] or in non–*KRAS*-driven

cancers,[33,48,49] *TP53* as a concurrent alteration in *KRAS* NSCLC does not seem to drive outcomes,[11,25,29,44,50] a finding recapitulated by the data presented here. When studied in more granular detail, it seems that there may be differential effects between missense and truncating alterations and that concomitant missense *TP53* mutations may lead to a paradoxical survival benefit when accompanied by *STK11* or *KEAP1* mutations.[33,44] The mechanism underlying this interesting finding is not yet well described, but it may involve complex interactions between mutant p53 and the NRF2 pathway. Other groups have indicated that a combination of co-mutations including *TP53* may confer a poorer risk than single co-mutations alone.[17] Because of low numbers of multiply occurring co-mutations, we were not able to investigate further the precise effect of *TP53* in combination with *STK11* or *KEAP1* mutations, but it is clear that this complex interplay requires further study.

Last, we explored the outcomes of patients with *SMARCA4* co-mutations given their significant prevalence in our sample. These alterations have been less studied in the context of *KRAS*-mutant NSCLC. On a molecular level, *SMARCA4* is involved in transcriptional regulation of gene expression promoting NSCLC development[51,52] and independently has been found to portend shorter OS both with and without treatment effect.[19,20,53,54] In *KRAS*-mutant NSCLC, one group had poorer response to IO,[55] though another exhibited improved survival with IO, perhaps related to higher TMB (though lower PD-L1 was often present).[19] In our cohort, patients with *SMARCA4* mutations had poorer PFS than wild type, though OS was not significantly different. Interestingly, Schoenfeld et al.[19] found that the deleterious effects of *SMARCA4* mutations persisted even if the mutation was nontruncating. Therefore, despite the fact that most our sample comprised nontruncating mutations, it seems possible that we could have captured the detrimental effect of *SMARCA4* mutations even in this small cohort.

The limitations of the study are chiefly that as a single-center retrospective study, we did not have sufficient power to stratify our analysis by treatment type. In addition, in analyzing real-world outcomes outside of the context of clinical trials, judgment of disease progression or stability was based on treating physician's judgment rather than from Response Evaluation Criteria in Solid Tumors data, though we reviewed radiographic reports to ensure concordance with the treating physician's judgment.

Nevertheless, this study is significant in that it reveals the differential outcomes on the basis of co-mutational pattern in patients with *KRAS* G12D-mutant NSCLC. The implications are clinically relevant and may affect how we counsel patients, how we select individualized treatment plans, and how we design studies. It is imperative that we understand as much as possible regarding the specific genomic landscape of individual tumors in the context of new drug development and in predicting potential response. Within the limitations of this single-center retrospective study, we found that the detrimental outcomes in patients with *KRAS* G12D-mutant NSCLC may be largely driven by co-mutational pattern, which may in turn indicate aggressiveness of disease and potential resistance to available standard chemotherapies and immunotherapies. Further validation is warranted in larger cohorts as we seek to further clarify the way forward for patients with *KRAS* G12D-mutated cancers.

CRediT Authorship Contribution Statement

Alissa J. Cooper: Conceptualization, Data curation, Investigation, Writing—original draft, Writing—review and editing.

Alona Muzikansky: Formal analysis, Methodology, Writing—review and editing.

Jochen Lennerz: Resources, Data curation, Writing—review and editing.

Farhaana Narinesingh: Data curation, Writing—review and editing.

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Rebecca S. Heist: Conceptualization, Methodology, Investigation, Supervision, Writing—review and editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100390.

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