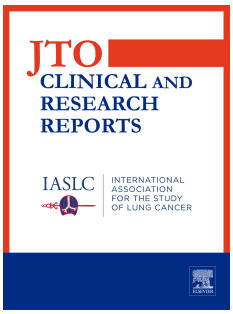

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Clinicopathologic characteristics and outcomes for patients with *KRAS* G12D-mutant non-small cell lung cancer

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Abstract (247/250 words)

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

107 patients with *KRAS* G12D-mutant NSCLC were identified. Most patients were former smokers (80, 74.8%) and had tumors with adenocarcinoma histology (93, 86.9%). Among 56 patients evaluated for PD-L1 expression, tumor proportion score was <50% in 43 (76.8%). Concomitant mutations were identified in *STK11* (17/107, 15.9%), *KEAP1,* (10/58, 17.2%), *TP53* (36/107, 33.6%), and *SMARCA4* (11/107, 10.3%). Among 57 patients treated with first-line therapy, patients with *STK11* co-mutations had shorter progression-free survival (PFS, 1.2 months, 95% CI 0.6 – 2.9, vs 4.1 months, 95% CI 2.5 – 6.0, $p = 0.0235$) and overall survival (OS, 4.3 months, 95% CI 1.2 – 10.6, vs 17.9 months, 95% CI 8.6 – 31.1, $p = 0.0018$) compared with wild-type. Patients with *KEAP1* co-mutations had shorter OS (4.6 months, 95% CI 1.2 – 10.6, vs 17.9 months, 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 impact survival.

Introduction

The ability to identify and therapeutically target oncogenic driver alterations is a cornerstone of the current treatment paradigm for non-small cell lung cancer (NSCLC).[1,2] Mutations in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene are among the most commonly 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 showing promising efficacy in preclinical studies[6] and are expected to soon enter clinical trials. This paper aims to describe the clinicopathologic characteristics of *KRAS* G12D lung cancer, as well as 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 significant gap in the literature and an understanding of how patients with G12D lung cancer fared prior to the advent of G12D specific inhibitors will be needed. Previous literature has demonstrated an association with never- or minimal smoking status,[13-16] as well as the potential for a poor prognosis compared with other *KRAS* mutation subtypes.[11,17] The co-mutational profile, which has emerged as a significant 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 biologic 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 assess the clinicopathologic characteristics and clinical outcomes of patients with NSCLC harboring *KRAS* G12D. Patients with NSCLC at 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 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 assess 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 via tumor proportion score (TPS). 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 prior data demonstrating 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%) (**Supplemental Figure 1**). Clinical, demographic, histologic, and molecular characteristics of patients with NSCLC are summarized in **Table 1**. Median age was 68 (range 29 - 90), and 59.8% were female. 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%). Twenty-seven of 75 patients had central nervous system metastases at any time. Histology for the majority of patients was adenocarcinoma (93, 86.9%). Analysis of co-mutation status demonstrated that 17

patients had co-occurring *STK11* mutations (15.9%) and 36 (33.6%) had *TP53* mutations. Among 58 pts 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%), 2 in *SMARCB1* (1.9%), and 4 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 <1% in 24 patients (22.4%), 1-49% in 19 patients (17.8%), and $\geq$ 50% in 13 patients (12.2%). **Figure 2** demonstrates a scatter plot of PD-L1expression by co-mutation. PD-L1 expression was similar amongst 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 metastatic patients

Of the 75 patients who had metastatic disease, 57 were treated with front-line systemic therapy; this consisted of chemotherapy alone in 29 (50.9%) patients, immunotherapy (IO) alone in 17 (29.8%), and combination chemotherapy and immunotherapy (chemo/IO) in 11 (19.3%). The majority of patients received one (24, 42.1%) or two (22, 38.6%) lines of therapy (range 1-7) **(Table 1)**. Treatment type by co-mutation status is displayed in **Table 2.** In our cohort, about half of the patients with each co-mutation were treated with chemotherapy alone, with the remaining patients receiving an immunotherapy-containing regimen (immunotherapy alone or chemo-immunotherapy).

First-line treatment was terminated for progression in 38 cases (66.7%) and for toxicity in 8 cases (14%). Other reasons for termination were identified in 5 cases (8.8%), including 2 (3.5%) in which treatment was stopped due to stable disease after two years of therapy. Information regarding reason for treatment termination was missing in 3 cases (5.3%), and treatment was ongoing at the time of this analysis for 3 patients (5.3%).

Progression-Free Survival

Median PFS among patients with metastatic disease treated with first line therapy was 3.0 months (95% CI 2.1– 5.1) with a median follow-up time of 2.84 months (**Figure 3A**). Analysis

by co-occurring mutational status suggested that *STK11* and *SMARCA4* mutations were associated with shorter PFS, while *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* wildtype (n = 47) (p= 0.0235) (**Figure 3B**). Patients with *SMARCA4* mutations (n = 8) also demonstrated shorter PFS than patients who had *SMARCA4*-wildtype disease (n = 49) (median PFS 1.5 months (95% CI 0.6 – 2.1) vs 4.0 months (95% CI 2.5 – 6.0), p = 0.0039) (**Figure 3C**). 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* wildtype (n = 32) (95% CI 1.5 – 6.0) (p = 0.1087) (**Figure 3D**). 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 months (95% CI 1.5 – 6.9) vs 2.8 months (95% CI 1.5 – 5.1), p = 0.7253) (**Figure 3E**).

Overall Survival

Median OS in all 75 patients with metastatic disease was 11.9 months (95% CI 8.0 – 23.3) 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 months (95% CI 8.1 – 27.4) (**Figure 4A**). 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) (**Figure 4B**). For patients with *KEAP1* mutations (n = 7), median OS was 4.6 months (95% CI 1.2 – 10.6) compared to 17.9 months (95% CI 7.1 – 30.1) in *KEAP1* wildtype (n = 32) (p = 0.0125) (**Figure 4D**). 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 months (95% CI 1.2 – 27.4) for patients with co-occurring *SMARCA4* mutations (n = 8) vs 17.3 months (95% CI 8.6 – 29.1) for patients with *SMARCA4* wildtype (n = 49) (p = 0.4202) (**Figure 4C**), and for patients with *TP53* mutations (n = 21), median OS was 10.6 months (95% CI 7.2 – 32.3) compared with 17.3 months (95% CI 5.9 – 29.1) for *TP53* wild-type (n = 36) (p = 0.4175) (**Figure 4E**).

Discussion

Here, we present detailed clinical, pathologic, 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, with one notable

exception: in contrast to prior 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 may indicate that the manifold contributions to tumorigenesis do not hinge simply on the presence or absence of tobacco smoke as a carcinogen exposure. However, the prevalence of co-occurring *STK11, KEAP1,* and *TP53* mutations in our dataset is similar to what has been reported elsewhere,[11,24,25] suggesting that our patient population, although small, is likely representative. In addition, the relatively low level of PD-L1 expression seen in the *KRAS* G12D/*STK11* mutated cohort recapitulates what has been seen 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* wildtype, while *TP53* mutations exerted no influence. Patients with co-occurring *KEAP1* mutations had worse OS; a statistically significant difference in PFS was not seen, although the numbers are small. Patients with *SMARCA4* mutations demonstrated 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 seen in *KRAS* mutated lung cancer, with alterations in *STK11*, *TP53*, and *KEAP1* defining distinct subtypes.[28]

A number of studies have demonstrated 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 demonstrated poorer response to treatment.[12,30,31] Similarly, *KEAP1* mutations have been shown to confer poorer outcomes both independent of[7] and related to treatment history[7,12,30,32] as well as in NSCLC without concurrent *KRAS* mutations.[33] As immunotherapy has emerged as the backbone of front-line 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 demonstrated that co-mutations in *STK11*[26,27,34,35] and *KEAP1*[27] are

associated with resistance to PD-1 blockade, worse PFS, and worse OS in *KRAS*-mutant lung cancer. Interestingly, when Ricciuti et al evaluated the effect of co-mutations among patients treated with first-line platinum chemotherapy, they found *STK11* and *KEAP1* mutations were associated with shorter PFS among *KRAS* mutant lung cancer, but not wildtype, in that setting as well. Our data are generally concordant with these results, though small sample size of the *KEAP1*-mutant patients limited our ability to detect a statistically significant difference in PFS for this population.

In our dataset we did not have sufficient power to separate the first-line treatment by IO alone or chemotherapy with IO. The findings of Ricciuti et al, 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 immunotherapy 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 shown to confer tumor survival advantage and promote an aggressive tumor subtype. Preclinical studies have demonstrated important differences in downstream signaling[41] and inflammatory microenvironment[18] based on *STK11* and *TP53* status, as well as on metabolic programming based on *STK11* and *KEAP1* mutations.[42,43] *KEAP1* mutations have been shown to confer chemoresistance to NSCLC cells in both *in vitro*[50] and murine model experiments,[39] which may translate to a shorter duration of chemotherapy 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 seen with traditional chemo- or immunotherapy 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 demonstrated 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.[44] This effect was not replicated in the evaluation of response by co-mutation in studies of sotorasib, and indeed it appeared that there was a numerically lower response rate in patients with *KEAP1*-mutant cancer compared with wild-type (20% vs 44%).[45] While it is unknown whether such differences would also be seen in patients with *KRAS* G12D

treated with G12D-specific therapy, the differential survival outcomes seen 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,[46] or in non-*KRAS* driven cancers,[33,47,48] *TP53* as a concurrent alteration in *KRAS* NSCLC does not seem to drive outcomes,[11,25,29,49,50] a finding recapitulated by the data presented here. When studied in more granular detail, it appears 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.[33,50] The mechanism underlying this interesting finding is not yet well described, but 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] Due to 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.

Lastly, 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 shown to portend shorter OS both with and without treatment effect.[19,20,53,54] In *KRAS*-mutant NSCLC, one group demonstrated poorer response to immunotherapy,[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 demonstrated poorer PFS than wild-type, though OS was not significantly different. Interestingly, Schoenfeld et al found that the deleterious effects of *SMARCA4* mutations persisted even if the mutation was non-truncating.[19] Therefore, despite the fact that the majority of our sample comprised non-truncating mutations, it appears 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 RECIST data, though we reviewed radiographic reports to ensure concordance with the treating physician's judgment.

However, this study is significant in that it demonstrates the differential outcomes based on co-mutational pattern in *KRAS* G12D-mutant NSCLC patients. The implications are clinically relevant, and may affect how we counsel patients, how we select individualized treatment plans, as well as 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 *KRAS* G12D-mutant NSCLC patients may be largely driven by co-mutational pattern, which may in turn indicate aggressiveness of disease and potential resistance to available standard chemo- 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.

Figures and Tables

Table 1. Characteristics of patients with *KRAS* G12D-mutant NSCLC

	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%)
Extra-thoracic 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*	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%)

Treatment lines	
One	24 (42.1%)
Two	22 (38.6%)
Three	4 (7.0%)
Four or more	7 (12.3%)

*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.
Abbreviations: CNS, central nervous system; mets, metastases; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor

Table 2. First-line systemic therapy amongst patients with metastatic *KRAS* G12D-mutant NSCLC by presence or absence of co-mutation

Co-mutation	Chemotherapy alone n (%)	Immunotherapy alone n (%)	Chemo-immunotherapy 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

Abbreviations: mut, mutated; WT, wild-type; unk, unknown

Supplementary Table 1. Co-mutations present in each patient's tumor sample with corresponding variant allele frequencies.

Pt	*STK11* mutation	*KEAP1* mutation	*TP53* mutation	*SMARCA4* mutation	Other mutations (known/likely oncogene	Other mutations (unk sig)

					/tumor suppressor)	
43	-	-	-	-	-	-
126	-	Gly333Val (0.8)	-	Trp764Leu* (0.8)	-	*IDH1* Arg20Ter (0.1), *TSC1* Arg336Trp (0.3), *RNF43* Arg117Pro (0.7)
127	-	-	-	-	*PIK3CA* Glu545Lys (0.1)	-
128	-	-	Gly266Val* (0.9)	Gln470Pro* (0.5)	*CDKN2A* intronic splice donor variant (0.8), *KRAS* gain	*ARID1A* Met1256Ile (0.2)
129	-	-	-	-	-	*MSH6* Ser611Arg (0.5), *BRCA1* intronic splice region variant (0.1)
130	Glu130Ter (0.2)	Cys171Tyr * (0.1)	-	Glu993Ter (0.2)	-	-
131	-	-	Arg273Pro (0.1), Glu198Ter (0.2)	-	-	*CCND2* Arg262Cys (0.3)
132	intronic splice acceptor variant c.921-1G>T (0.6)	Arg483Leu * (0.5)	-	Met272Cysfs Ter31 (0.5)	*CDKN2A* loss	-
133	-	-	intronic splice donor variant c.375+1G> A (0.3)	-	-	*CIC* Arg1364Trp (0.3)
134	-	-	-	-	-	*KIT* splice region

						variant (0.1)
135	-	-	-	-	*NF1* Thr2061Hisfs Ter9 (0.1), *SMAD4* Arg502del (0.1)	*STAG2* Gly846Val (0.2), *NF1* Ala2441Ser (0.2)
136	intronic splice acceptor variant c.281-2A>T (0.5)	Thr142Ile* (0.4)	-	-	-	*TP63* Glu63Ter (0.1)
137	His174Leu (0.1)	His436Arg* (0.3)	-	-	-	*ATM* Gly2180Ala (0.3), *MAP3K1* Lys64Glu (0.2)
138	-	-	-	-	-	
139	-	Gly603Arg* (0.3)	-	Ala1158Val* (0.3)	-	*APC* Ala2274Val (0.4), *ABL1* Gly250Val (0.3), *VHL* Glu21Ala (0.3), *RB1* Gln736Glu (0.2)
140	Gln37Ter (0.2)	-	-	Thr308Met* (0.2)	*CDKN2A* Arg99Gln (0.5), *CCND2* gain	*SDHB* intronic splice donor variant (0.1)
141	-	-	-	-	-	-
142	-	-	-	-	-	-
143	-	-	Gly266Ter (0.4)	-	-	-
144	-	-	-	-	*APC* Ser1465Argfs Ter9 (0.01)	*BRCA2* Arg2108Cys (0.6)
145	-	-	-	-	-	-
146	-	-	-	-	-	-

147	intronic splice acceptor variant c.598-2A>G (0.4)	Ser104Ile* (0.2)	-	Leu1163Arg* (0.4)	*CTNNB1* Ser37Cys (0.3)	*MET* Ala347Thr (0.2), *TSC1* Pro114Ser (0.4)
148	-	-	-	-	-	-
149	-	-	-	-		*ATM* Val1464Asp (0.2)
150	-	-	-	-	-	-
151	-	-	-	-	-	-
152	-	-	-	-	-	-
153	-	-	-	-	*CCND1* gain, *FGF19* gain	*ATM* Tyr454Ter (0.1)
154	Asp194Tyr (0.3)	MetAla94IleSer* (0.3)	-	-	*MYC* gain	*ATM* intronic splice region variant (0.2)
155	-	-	Gly244Arg (0.2)	-	*NF1* HisGln588GlnTer (0.3), *CDKN2A* Tyr44Ter (0.2)	-
156	-	-	-	-	*TERT* promoter chr5 g.1295228G>A (0.1)	-
157	Tyr60Ter (0.2)	-	-	-	-	*SMAD4* Leu533dup (0.3), *BRCA1* intronic splice acceptor variant (0.2)
158	-	-	-	-	-	-
159	-	-	-	-	-	-
160	-	-	-	-	*NKX2-1* gain	*DDX3X* Asp219Glu (0.5), *CIC* Arg1275Cys (0.2), *SMARCB1*

						Gln120Ter (0.2)
161	Pro275ArgfsTer12 (0.1)	-	-	-	-	-
162	-	-	Arg273Leu (0.3)	-	*KRAS* gain	*TERT* promoter variant (0.1)
163	-	-	-	-	*PIK3CA* Glu453Lys (0.3)	*APC* Arg876Gln (0.3)
164	-	-	Arg283Cys (0.7), Met246Val (0.4)	Arg1192Leu (0.5)	-	*STAG2* Cys127Phe (0.6)
165	-	-	-	-	-	
166	-	-	-	-	*ARID1A* Glu2250ValfsTer27 (0.2), *CDKN2A* Met52AspfsTer67 (0.1)	*RNF43* Ile209Met (0.4)
167	-	-	Gly245Ser (0.1)	Thr1034Ile* (0.5)	*GNAS* Arg201His (0.1), *PIK3CA* Gln546Pro (0.1), *CDKN2A* Tyr44Ter insertion (0.2)	*RHOA* Asp65Tyr (0.1)
168	-	-	Tyr205Cys (0.04)	-	*PIK3CA* Glu453Lys (0.1)	-
169	-	-	Arg306Ter (0.3)	Arg1077Gln* (0.3), Arg1087Thr* (0.3), Met1105Ile* (0.2)	*BRAF* Asp594Asn (0.1)	-
170	-	-	-	-	-	*SMO* Ala540Thr

						(0.2), *PTCH1* Val11081Met (0.5), *STAG2* Ser843Ile (0.1)
171	-	-	-	-	*ARID1A* Ser233GlufsTer165 (0.1, 0.04)	-
172	intronic splice donor variant c.374+1A>G (0.4)	Gly430Val (0.4)	intronic splice donor variant c.559 1G>T (0.4)	-	*ARID1A* Gln528Ter (0.2), *CDKN2A* loss	*TP63* Gln20Lys (0.2), *SMO* Arg451His (0.1), *ERBB4* Pro610Ser (0.2), *FLT3* Leu983Val (0.3), *APC* Arg2393Thr (0.4), *ATRX* Pro657HisfsTer3 (0.2)
173	-	-	Tyr236Cys (0.3)	-	*MSH6* Tyr103Lysfs (0.4), *NKX2-1* His319ProfsTer90 (0.4)	-
174	Glu165SerfsTer122 (0.5)	-	-	-	-	*CTNNB1* Asp6Val (0.3), *ERBB4* Gly223Val (0.2), *ERBB4* possible splice region/ intronic variant (0.2)
176	-	-	Gly154Val (0.2)	-	-	-
177	SerIle299PheMet* (0.6)	-	Lys291GlufsTer3 (0.4)	Leu1126Pro* (0.7)	*CDKN2A* loss	*ATM* Ile389Val (0.6), *ATM* Glu2272Lys (0.5), *RB1* Ala201Pro

						(0.5), *ATRX* intronic splice region variant (0.3)
178	Lys48Ter (0.03)	-	-	-	*FGFR3* loss	*SMARCB1* Arg40Ter (0.1)
179	-	-	-	-	*NOTCH1* loss, *TSC2* loss	*BRCA1* Asp560Ala (0.2)
180	-	Lys303_Phe305del* (0.1)	Glu56Ter* (0.1)	-	*CDKN2A* intronic splice acceptor variant (0.1)	*BRCA2* Arg2432Thr (0.1), *MYC* Arg398Leu (0.1), *ERBB3* Ser336Phe (0.1), *CCNE1* intronic splice region variant (0.1)
181	-	-	Gly244Asp (0.6)	-	*MYC* gain, *CDKN2A* loss, *NKX2-1* loss, *KRAS* gain	*CDH1* Glu482Lys (0.4), *ATM* Asp1215Val (0.2), *PIK3R1* intronic splice region variant (0.4)
182	-	-	-	-	*FGFR3* loss, *TSC2* loss	-
183	-	-	Glu343Lys* (0.2), Lys139Asn (0.3)	-	*PTEN* Gln245Ter (0.2), *MYC* gain	-
184	-	-	-	-	*NKX2-1* insertion (0.2)	-
207	-	NA	Tyr234Cys (0.2)	-	-	-
209	-	NA	Arg273Leu (0.4),	-	*CTNNB1* Ser37Phe	-

			Cys135Tyr (0.2)		(0.2)	
210	-	NA	-	-	-	
211	-	NA	Glu336Ter (0.1)	-	-	*DDR2* intronic splice acceptor variant (0.1)
212	-	NA	-	-	-	*SMAD4* Leu535_Asp537delinsHis (0.5), *SMAD4* Asp537His (0.5)
213	-	NA	Glu204Ter (NA)	-	-	-
214	Glu199Ter (0.2)	NA	-	-	-	-
215	-	NA	-	-	-	-
216	Lys78Glu (0.2)	NA	Ser241Pro (0.192727), Leu93fs (0.1)	-	-	*APC* Glu893Lys (0.5)
217	-	NA	-	-	-	*GNAS* Arg844His (0.1), *KIT* Phe508Ile (0.5)
218	-	NA	Glu287fs (0.1)	-	-	-
219	-	NA	Glu224Ter (0.1)	-	*PIK3CA* Glu542Gln (0.1), *SMAD4* Ser144Ter (0.1)	-
220	-	NA	-	-	-	-
221	-	NA	His214Arg (0.1, 0.1)	-	-	-
222	-	NA	-	-	-	-

224	-	NA	-	-	-	-
225	-	NA	-	-	-	-
226	-	NA	-	-	-	-
227	-	NA	-	-	-	-
228	Lys78Asn (0.072664) Arg415His* (0.19084)	NA	-	-	-	-
229	-	NA	Gly244Ser (0.2), Asp324His* (0.2)	-	*CDKN2A* Gly35Trp (0.4)	-
230	-	NA	-	-	-	-
231	-	NA	-	-	-	-
232	-	NA	-	-	-	*NOTCH1* Gly2427Ser (0.6)
233	-	NA	-	-	-	*GNAS* Arg844His (0.1)
234	-	NA	-	-	-	
235	-	NA	Pro152fs (0.2)	-	*CDKN2A* Arg24fs (0.2)	*MET* Val1359Ile (0.1)
236	-	NA	-	-	*CTNNB1* Thr41Ala (0.1)	-
237	-	NA	-	-	-	-
238	-	NA	-	-	-	-
239	-	NA	-	-	-	-
240	-	NA	-	-	-	-
241	-	NA	-	-	-	-
242	-	NA	-	-	-	-
243	-	NA	-	-	*KRAS* G12C (0.1)	*APC* Gln1230Arg (0.5)
244	-	NA	Arg158Ser (0.1)	-	-	-
245	-	NA	-	-	-	-
246	Cys132Trp (0.5)	NA	-	-	-	-
247	-	NA	Arg248Gln	-	-	*GNAS*

			(0.4)			Arg844Ser (0.2)
248	-	NA	Arg110Leu (0.1)	-	-	*ALK* Arg1192Trp (0.5), *IDH2* Arg140Gln (0.1)
249	-	NA	-	-	-	-
250	-	NA	-	-	-	-
251	-	NA	Tyr205Cys (0.1)	-	-	-
252	-	NA	His179Arg (0.6)	-	-	-
253	-	NA	Pro278Leu (0.4)	-	*PIK3CA* Glu542Lys (0.1)	-
254	-	-	splice donor variant c.987_993 5del* (0.1)	-	-	-
255	-	NA	Arg175His (0.1)	-	-	-
256	-	NA	Arg282Pro (0.1)	-	-	-

Abbreviations: unk = unknown; sig = significance; NA = not available

*denotes co-mutations of unknown oncogenic significance

Supplementary Table 2. Variant allele frequencies of *KRAS* G12D mutation in each patient's tumor sample(s).

Pt	Variant allele frequencies
43	0.1, 0.2, 0.1, 0.1
126	0.3
127	0.4
128	0.8

129	0.3
130	0.1
131	0.4
132	0.3
133	0.3
134	0.1
135	0.1
136	0.4
137	0.3
138	0.2
139	0.4
140	0.4
141	0.2
142	0.1
143	0.5
144	0.1
145	0.02
146	0.01
147	0.2
148	0.4
149	0.4, 0.4
150	0.1
151	0.1
152	0.04
153	0.5
154	0.4
155	0.2
156	0.3
157	0.5
158	0.1
159	0.1
160	0.4
161	0.1

162	0.8
163	0.2
164	0.3
165	0.1
166	0.2
167	0.1
168	0.1
169	0.3
170	0.3
171	0.1, 0.1
172	0.4
173	0.3
174	0.3
176	0.3
177	0.8
178	0.02
179	0.2
180	0.1
181	0.8
182	0.03
183	0.4
184	0.2
207	0.2
209	0.4
210	0.1
211	0.2
212	0.1
213	0.3
214	0.1
215	0.3
216	0.1
217	0.1
218	0.1

219	0.1
220	0.1
221	0.2, 0.1
222	0.1, 0.1
224	0.1
225	0.1
226	0.1
227	0.02
228	0.1
229	0.4
230	0.4
231	0.2
232	0.1
233	0.1
234	0.2
235	0.4
236	0.1
237	0.2
238	0.2
239	0.3
240	0.2, 0.3
241	0.04, 0.1
242	0.1
243	0.03
244	0.1
245	0.2
246	0.3
247	0.5
248	0.5
249	0.04
250	0.4
251	0.1
252	0.3

253	0.5
254	0.2
255	0.1
256	0.1

FIGURE LEGENDS

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.

Figure 2. Association of PD-L1 level with molecular alterations

Scatterplot of percent expression of PD-L1 (y-axis) is shown in relationship to molecular wild-type (blue circles) or mutant (red triangles) status. PD-L1 expression was similar amongst wild-type and mutant for *TP53* and *SMARCA4* mutations, but relatively lower in *STK11*- and *KEAP1*-mutant samples compared with wild-type.

Abbreviations: PD-L1, programmed death ligand 1

Figure 3. Median progression-free survival (PFS) among patients with metastatic disease treated with first line therapy

PFS of the overall population is shown (A), as well as 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.

Figure 4. Median overall survival (OS) among patients with metastatic disease treated with first line therapy

OS of the overall population is shown (A), as well as 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.

Supplementary Figure 1. Relative frequency of *KRAS* G12D-mutant cancers

This chart depicts the relative frequency of *KRAS* G12D-mutant cancers in our cohort of 665 patients. Most patients had gastrointestinal cancers, and 107 had non-small cell lung cancer (16.1%).

Supplementary Figure 2. First-line treatment of patients with metastatic disease. This flow chart depicts the number of patients who received chemotherapy, immunotherapy, and chemo-immunotherapy as first-line treatments, followed by how many patients went on to receive two or more lines of therapy.

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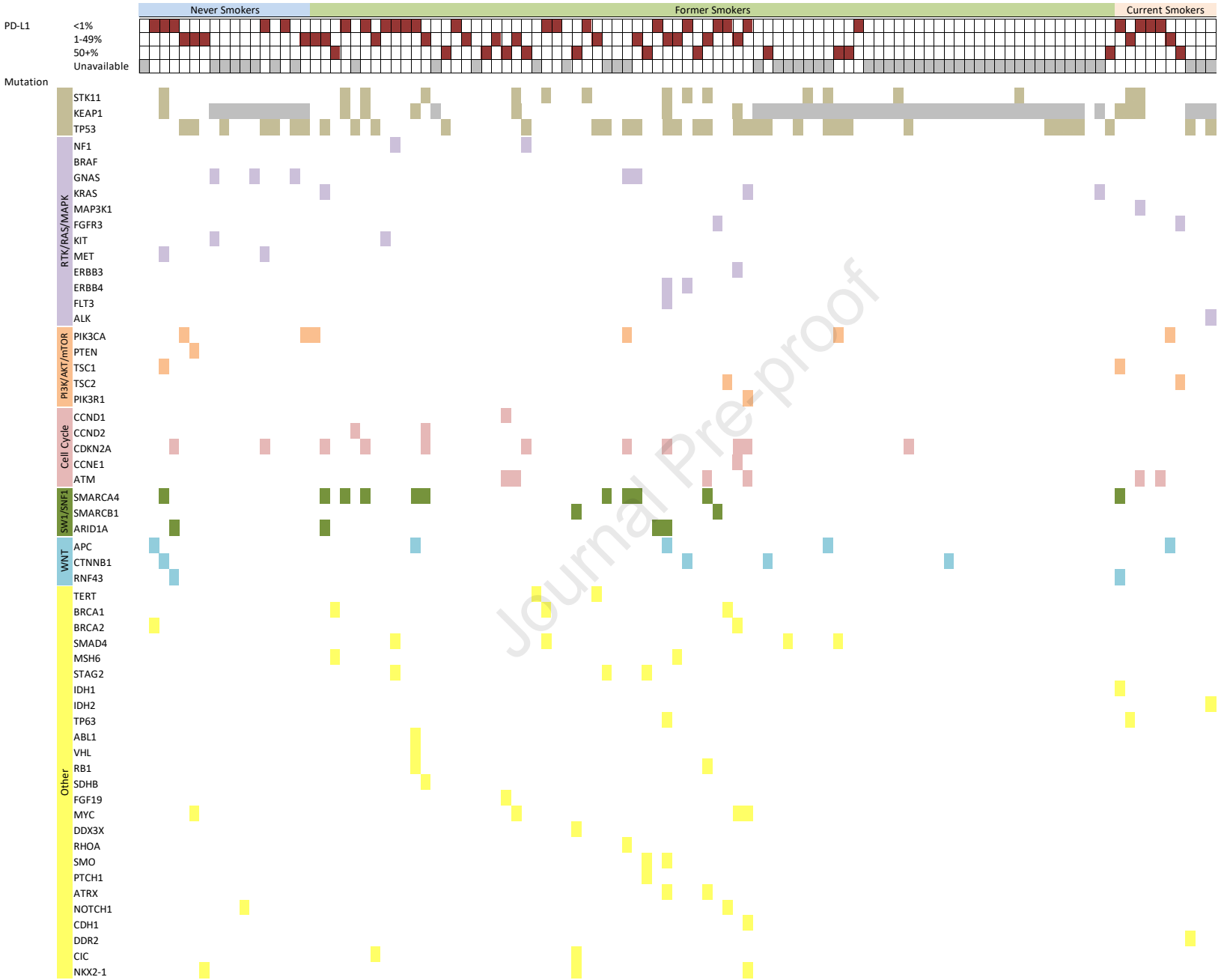

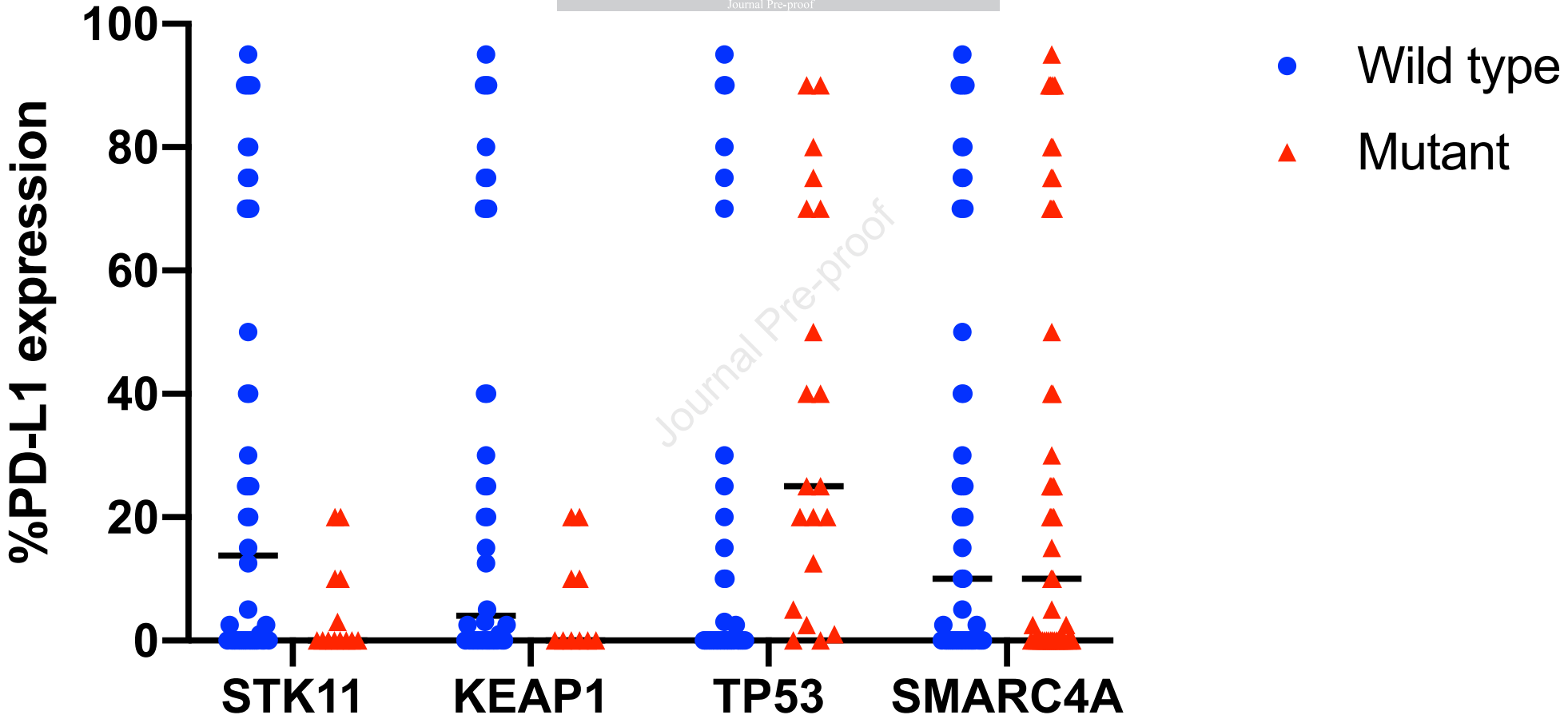

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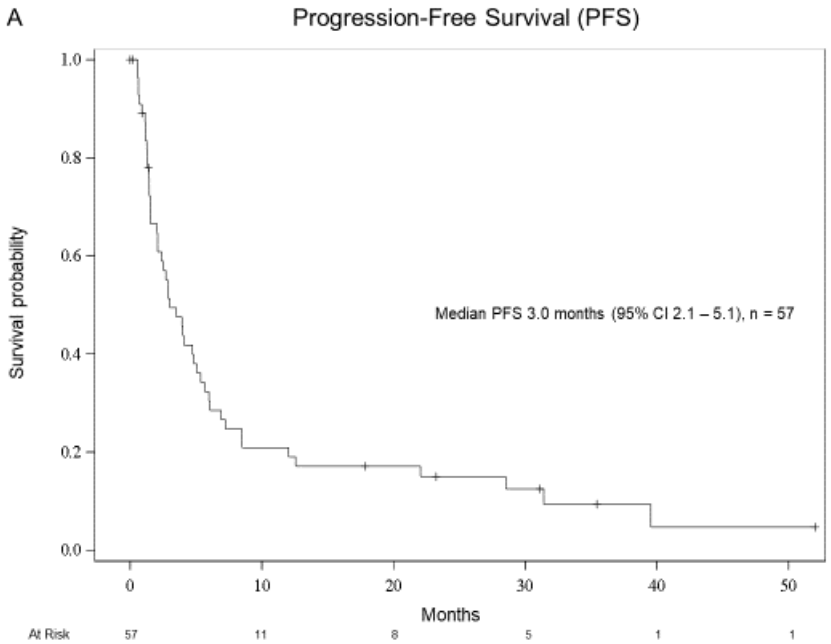

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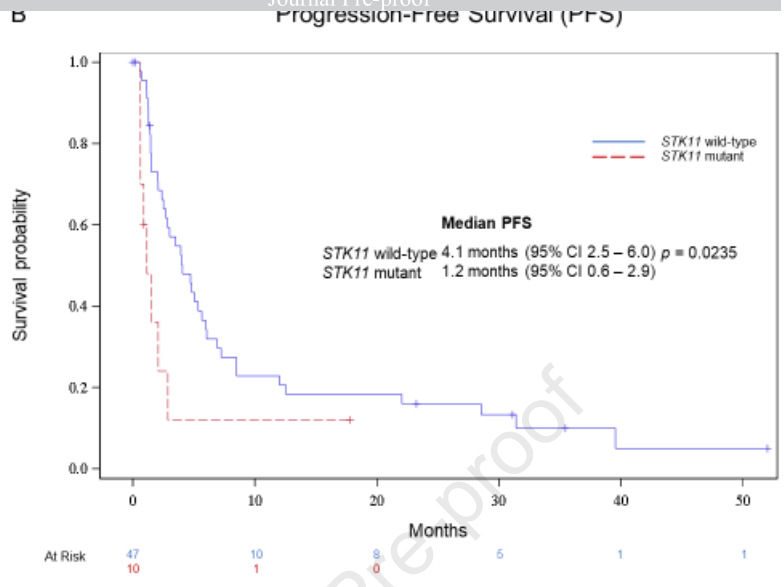

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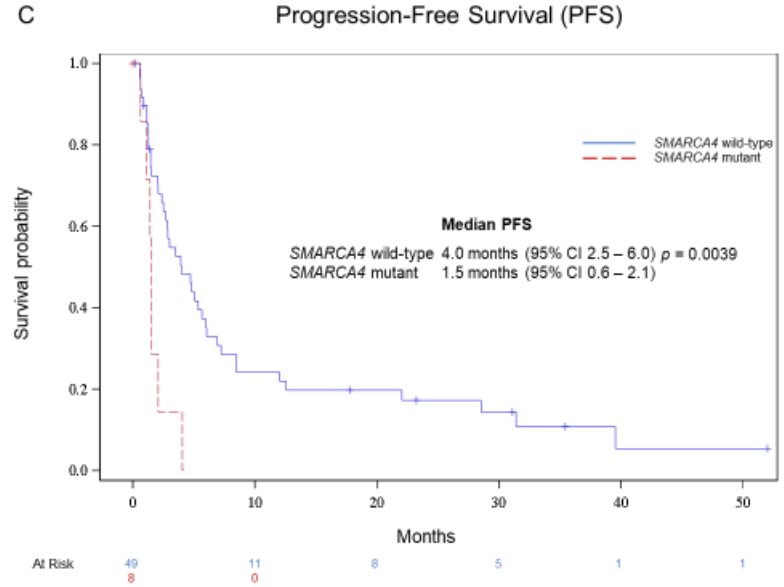

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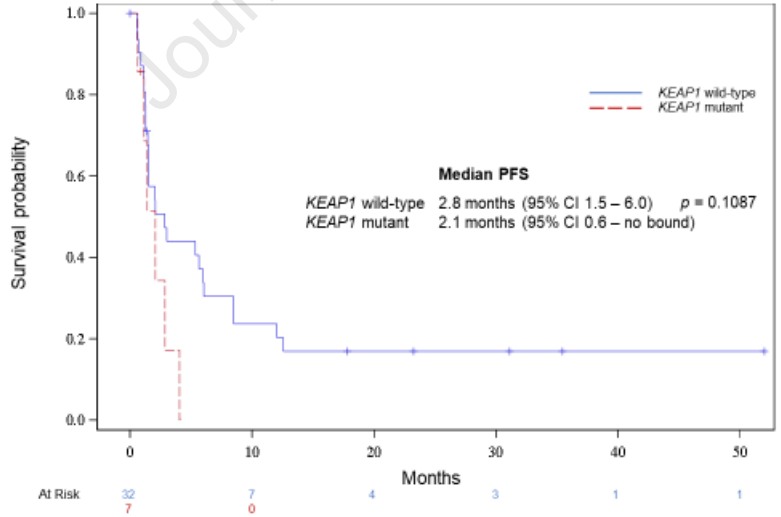

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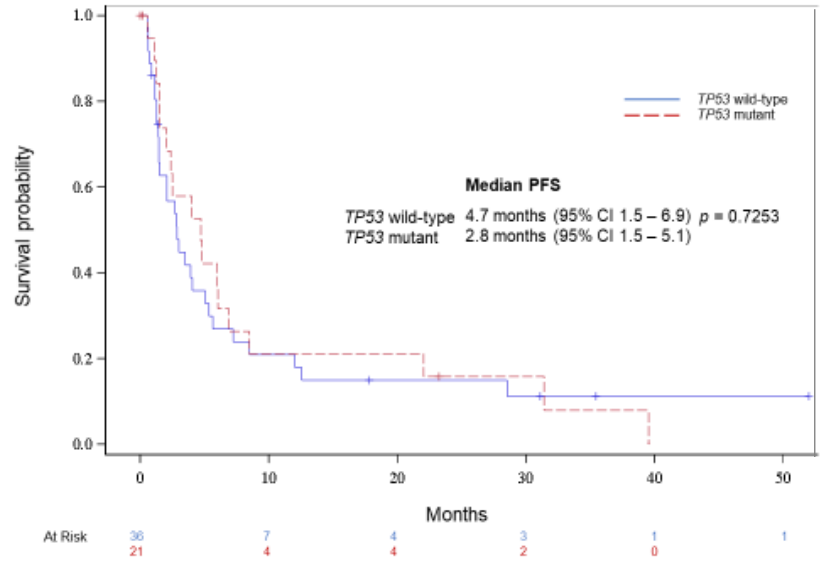

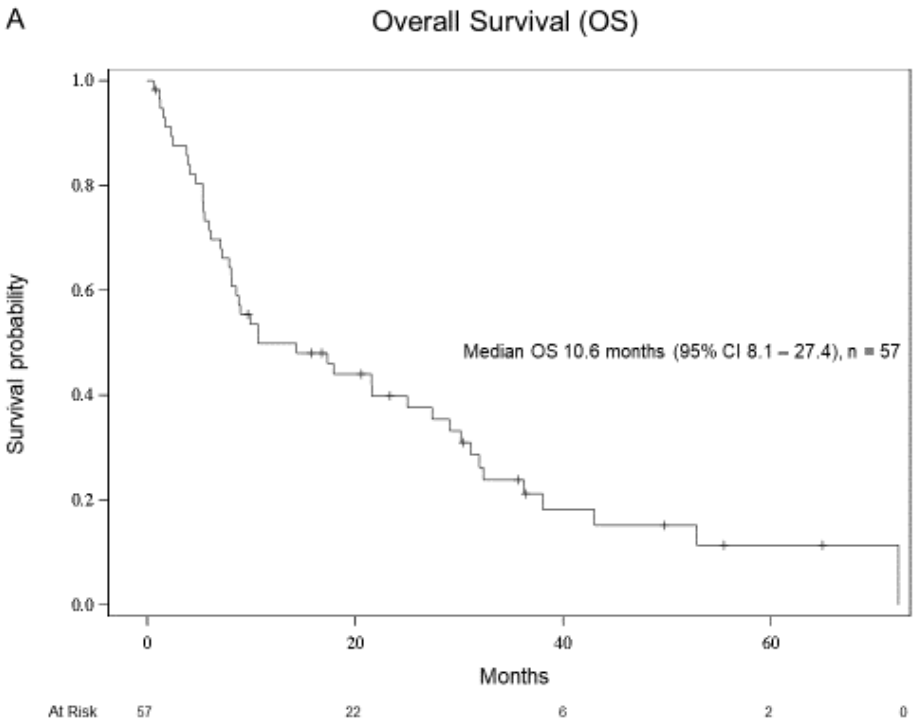

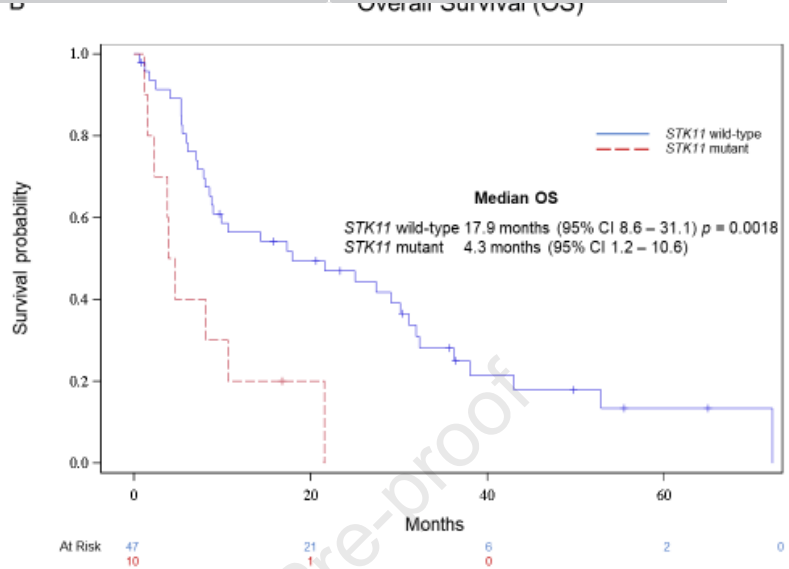

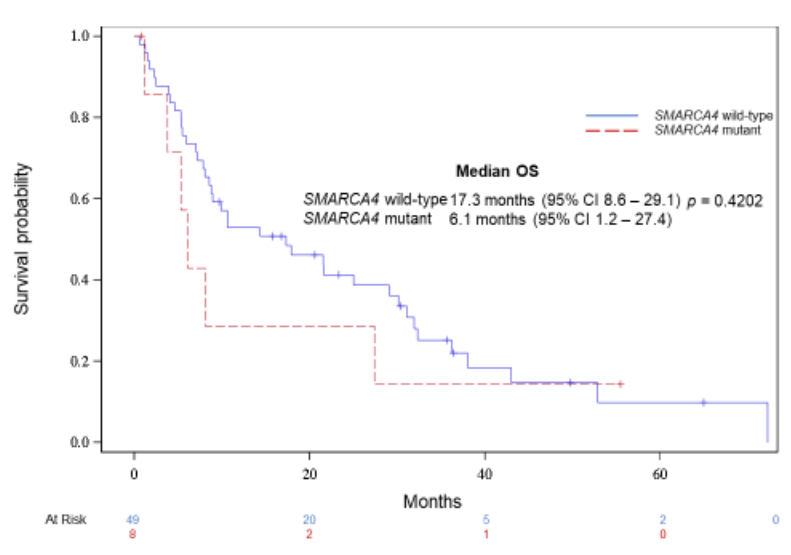

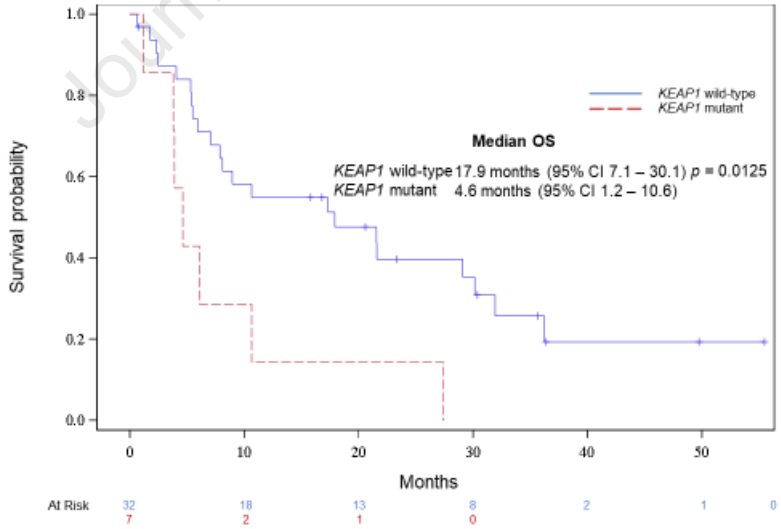

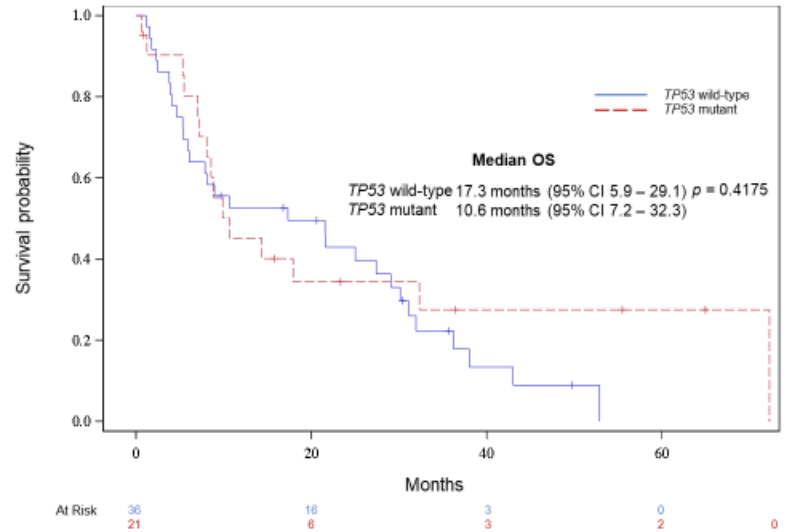

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