# Brief Report: Not Created Equal: Survival Differences by *KRAS* Mutation Subtype in NSCLC Treated With Immunotherapy

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Received 21 June 2024; revised 11 October 2024; accepted 21 October 2024
Available online - 24 October 2024

**ABSTRACT**

**Introduction:** The predictive and prognostic implications of different *KRAS* mutation (*KRAS*m) subtypes in metastatic NSCLC have not been clearly defined. We used a nationwide observational database to investigate whether *KRAS*m subtypes differ in their association with survival in metastatic NSCLC treated with immune checkpoint inhibitor (ICI)-based therapy, across programmed death-ligand 1 (PD-L1) levels.

**Methods:** Patients with advanced nonsquamous NSCLC who initiated first-line ICI-based therapy from 2016 to 2021 and had known PD-L1 expression and comprehensive genomic profiling including *KRAS*, *STK11*, *KEAP1*, and *TP53* were included. Within PD-L1 expression subgroups (<1%, 1%–49%, ≥50%), Cox multivariable regression was used to evaluate the association between *KRAS*m subtypes (G12C, G12V, G12D, other *KRAS*m) and overall survival, estimated using Kaplan-Meier methodology.

**Results:** Among the 1539 patients, 819 patients were *KRAS* wild type (*KRAS*wt) and 720 were *KRAS*m (296 *KRAS* G12C, 143 *KRAS* G12V, 97 *KRAS* G12D, 184 other *KRAS*m). In the 50% or higher PD-L1 subgroup, patients with *KRAS* G12V had worse survival (median overall survival [mOS] = 8.2 mo) compared with *KRAS*wt (mOS = 13.3 mo) and other *KRAS* subgroups (mOS ranging from 13.4 to 19.9 mo). On adjusted Cox multivariable regression in the 50% or higher PD-L1 subgroup, the hazard ratio for death for *KRAS* G12V ranged from 1.53 to 1.78 compared with *KRAS*wt and other *KRAS*m subtypes (all $p < 0.05$).

**Conclusions:** Although patients with 50% or higher PD-L1 with *KRAS* G12C, G12D, and other subtypes exhibited similar survival to *KRAS*wt, *KRAS* G12V was associated with significantly worse survival than *KRAS*wt and other *KRAS*m subtypes. All *KRAS*m should not be regarded as uniform predictors of ICI responsiveness, even with high PD-L1 expression; *KRAS* G12V tumors may have worse outcomes with ICI-based therapy and benefit from treatment intensification.



*Keywords:* NSCLC; Immunotherapy; *KRAS* mutation

## Introduction

*KRAS* mutation (*KRAS*m) is the most common alteration in metastatic NSCLC (mNSCLC), occurring in 20% to 40% of lung adenocarcinomas, and is associated with smoking history, high mutational and neoantigen burden, and responsiveness to immune checkpoint inhibitors (ICIs). We previously reported that *KRAS*m is associated

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**Cite this article as: Sun L, Zhou Y, Handorf EA, Borghaei H, Bauman J, Aggarwal C. Brief report: not created equal: survival differences by *KRAS* mutation subtype in NSCLC treated with immunotherapy. *JTO Clin Res Rep*. 2025;6:100755.**



**ISSN: 2666-3643**

**https://doi.org/10.1016/j.jtocrr.2024.100755**

with favorable survival with ICI monotherapy in programmed death-ligand 1 (PD-L1) high tumors,[1] and conversely that *KRAS*m is associated with poor survival in PD-L1 negative tumors, driven by enrichment in STK11 and KEAP1 commutations.[2] Although the targeted therapies involving sotorasib and adagrasib are approved in the second line setting for *KRAS* G12C mNSCLC, other distinct *KRAS*m subtypes (e.g., G12V, G12D) currently lack Food and Drug Administration–approved targeted therapies, though clinical trials investigating *KRAS* subtype-specific and pan-*KRAS* inhibitors are underway.

Predictive and prognostic implications of *KRAS*m subtypes in different disease and treatment settings have not been clearly defined. Several studies have shown that different *KRAS* subtypes may impart variable therapeutic responsiveness[3] and survival.[4] In the BATTLE trial which randomized patients to various targeted therapies, *KRAS* G12C and G12V were associated with shorter progression-free survival compared with other *KRAS* subtypes or wild-type *KRAS*.[5] *KRAS* codon 13 mutations have been shown to confer worse prognosis after adjuvant platinum chemotherapy[6] and possibly in the metastatic setting, though this result was not replicated in an independent validation cohort.[7] *KRAS* G12D has also emerged as a distinct subtype characterized by lower pack-year smoking history, lower PD-L1 expression, lower tumor mutational burden, and worse outcomes with PD-L1 inhibitor monotherapy.[8] Other studies have failed to find significant survival differences by *KRAS*m subtypes.[9,10] Ultimately, conclusions drawn from this body of work are limited by small sample sizes and heterogeneity in cancer stage and treatment type (chemotherapy versus immunotherapy versus targeted therapy), and incomplete PD-L1 biomarker data. Thus, an important relevant contemporary question—whether *KRAS*m subtype impacts survival outcomes in patients with mNSCLC treated with immunotherapy-based frontline therapy, across PD-L1 strata— remains incompletely understood.

To address this knowledge gap, we used a large real-world database to investigate whether *KRAS*m subtypes differ in their association with survival in mNSCLC treated with ICI-based therapy, across PD-L1 levels.

## Materials and Methods

This retrospective study used the nationwide de-identified Flatiron Health/Foundation Medicine clinicogenomic database and included patients from approximately 265 to 280 U.S. cancer clinics with advanced nonsquamous NSCLC who initiated first-line ICI-based therapy with or without chemotherapy between 2016 and 2021. Longitudinal clinical data were derived from electronic health record data, comprising patient-level structured and unstructured data, curated by means of technology-enabled abstraction, and linked to genomic data derived from Foundation Medicine Inc. (FMI) comprehensive genomic profiling tests in the Flatiron Health/Foundation Medicine clinicogenomic database by de-identified, deterministic matching.[11] Genomic alterations were identified by means of comprehensive genomic profiling of more than 300 cancer-related genes on FMI's next-generation sequencing test (FMI sequencing platform(s), that is, FoundationOne CDx, FoundationOne or FoundationOne Liquid, FoundationOneLiquid CDx dependent on the baitsets that were used for the study). The data were de-identified and subject to obligations to prevent re-identification and protect patient confidentiality.

Eligible patients had known PD-L1 expression levels and underwent genotyping that included *KRAS*, *STK11*, *KEAP1*, and *TP53* within 3 months of starting therapy. Patients with *EGFR* mutations, anaplastic lymphoma kinase, or *ROS1* translocations were excluded. Chi-square/analysis of variance and *t* test were used to compare baseline characteristics between patients with *KRAS* wild type (*KRAS*wt) and *KRAS*m tumors, and among G12C, G12V, G12D, and other *KRAS*m subgroups.

Real-world overall survival (OS) was estimated using the Kaplan-Meier methodology, with the left truncation method to adjust for situations in which molecular profiling may occur after the start of first-line treatment.[12] Within PD-L1 expression subgroups ($<$1%, 1%–49%, $\geq$50%), Cox multivariable regression was used to evaluate the association between *KRAS*m subtype and survival, adjusting for potential confounders (age, sex, race, year, histologic type, smoking history, performance status, treatment, and practice type, and STK11/KEAP1/TP53 commutations). Pairwise comparisons between *KRAS*wt and *KRAS*m subtype groups were calculated by means of linear combinations.

All statistical tests were conducted using R version 4.2. The *p* values of 0.05 or less were considered statistically significant. This study was granted a waiver of informed consent by the institutional review board of the University of Pennsylvania.

## Results

Of 2,593 patients who initiated immunotherapy-based treatment for NSCLC from 2016 to 2021 and had a Foundation Medicine sequencing assay with no mutations in EGFR, anaplastic lymphoma kinase, or ROS1, we excluded 1054 patients who either had squamous histologic type, missing PD-L1 or mutational status. Thus, our analytical cohort consisted of 1539 patients, of whom 819 were *KRAS*wt and 720 were *KRAS*m (296 *KRAS* G12C, 143 *KRAS* G12V, 97 *KRAS* G12D, 184 other *KRAS*m). Baseline demographics

**Table 1.** Baseline Characteristics

| Characteristic | *KRAS*wt (n= 819) | All *KRAS*m (n = 720) | *p* Value[a] | *KRAS* G12C (n = 296) | *KRAS* G12V (n = 143) | *KRAS* G12D (n = 97) | Other *KRAS*m[b] (n = 184) | *p* Value[c] |
|---|---|---|---|---|---|---|---|---|
| Mean age at diagnosis (SD) | 68.8 (9.5) | 69.2 (9.7) | 0.415 | 69.5 (9.8) | 68.9 (10.1) | 691 (9.6) | 68.8 (9.3) | 0.851 |
| Female | 364 (44.4) | 416 (57.8) | <0.001 | 172 (58.1) | 91 (63.6) | 48 (49.5) | 105 (57.1) | <0.001 |
| Race | | | 0.881 | | | | | 0.868 |
| Black or African American | 64 (7.8) | 52 (7.2) | | 19 (6.4) | 10 (7.0) | 5 (5.2) | 18 (9.8) | |
| Other/unknown | 201 (24.5) | 174 (24.2) | | 77 (26.0) | 34 (23.8) | 21 (21.6) | 42 (22.8) | |
| White | 554 (67.6) | 494 (68.6) | | 200 (67.6) | 99 (69.2) | 71 (73.2) | 124 (67.4) | |
| ECOG performance status | | | 0.882 | | | | | 0.039 |
| 0/1 | 561 (68.5) | 495 (68.8) | | 200 (67.6) | 105 (73.4) | 59 (60.8) | 131 (71.2) | |
| 2+ | 125 (15.3) | 104 (14.4) | | 51 (17.2) | 15 (10.5) | 10 (10.3) | 28 (15.2) | |
| Missing | 133 (16.2) | 121 (16.8) | | 45 (15.2) | 23 (16.1) | 28 (28.9) | 25 (13.6) | |
| History of smoking | 720 (87.9) | 686 (95.3) | <0.001 | 293 (99.0) | 131 (91.6) | 84 (86.6) | 178 (96.7) | <0.001 |
| Practice type | | | 0.689 | | | | | 0.569 |
| Academic | 67 (8.2) | 63 (8.8) | | 21 (7.1) | 13 (9.1) | 12 (12.4) | 17 (9.2) | |
| Community | 752 (91.8) | 657 (91.2) | | 275 (92.9) | 130 (90.9) | 85 (87.6) | 167 (90.8) | |
| Histologic type | | | 0.187 | | | | | 0.526 |
| Adenocarcinoma | 769 (93.9) | 687 (95.4) | | 286 (96.6) | 135 (94.4) | 92 (94.8) | 174 (94.6) | |
| Non-squamous, NOS | 50 (6.1) | 33 (4.6) | | 10 (3.4) | 8 (5.6) | 5 (5.2) | 10 (5.4) | |
| PD-L1 expression | | | 0.001 | | | | | 0.033 |
| 0% | 291 (35.5) | 197 (27.4) | | 78 (26.4) | 44 (30.8) | 28 (28.9) | 47 (25.5) | |
| 1%–49% | 239 (29.2) | 218 (30.3) | | 95 (32.1) | 40 (28.0) | 32 (33.0) | 51 (27.7) | |
| ≥50% | 289 (35.3) | 305 (42.4) | | 123 (41.6) | 59 (41.3) | 37 (38.1) | 86 (46.7) | |
| Treatment Category | | | 0.546 | | | | | 0.306 |
| Anti-PD-L1 monotherapy | 268 (32.7) | 253 (35.1) | | 113 (38.2) | 51 (35.7) | 27 (27.8) | 62 (33.7) | |
| Anti-PD-L1 + anti-CTLA-4 | 15 (1.8) | 15 (2.1) | | 7 (2.4) | 2 (1.4) | 0 (0.0) | 6 (3.3) | |
| Chemoimmunotherapy | 536 (65.4) | 452 (62.8) | | 176 (59.5) | 90 (62.9) | 70 (72.2) | 116 (63.0) | |
| STK11 mutation | 152 (18.6) | 205 (28.5) | < 0.001 | 84 (28.4) | 41 (28.7) | 22 (22.7) | 58 (31.5) | < 0.001 |
| KEAP1 mutation | 197 (24.1) | 165 (22.9) | 0.600 | 64 (21.6) | 31 (21.7) | 15 (15.5) | 55 (29.9) | 0.071 |
| TP53 mutation | 582 (71.1) | 349 (48.5) | < 0.001 | 159 (53.7) | 61 (42.7) | 44 (45.4) | 85 (46.2) | < 0.001 |

*Note:* All values are n (%) unless otherwise specified.

[a]Comparison between all *KRAS*m subtypes and *KRAS*wt (*t* test for continuous variables, chi-square for categorical).

[b]Other *KRAS*m consist of G12A (57), Q61H (31), G13C (21), G13D (21), G12S (10), G12R 9), G12F (8), Q61L (4), Q22K (3), A146V (2), Q61K (2), A146P (1), A146T (1), A59E (1), A59T (1), D173H (1), G10_A11insG (1), G12E (1), G12Y (1), G13F (1), G13V (1), K184T (1), L19F (1), L79F (1), Q61R (1), R164Q (1), V14L (1).

[c]Comparison between *KRAS* subtypes (*t* test for continuous variables, ANOVA for categorical).

ANOVA, analysis of variance; ECOG, Eastern Cooperative Oncology Group; *KRAS*m, *KRAS* mutation; *KRAS*wt, *KRAS* wild type; NOS, not otherwise specified; PD-L1, programmed death-ligand 1.

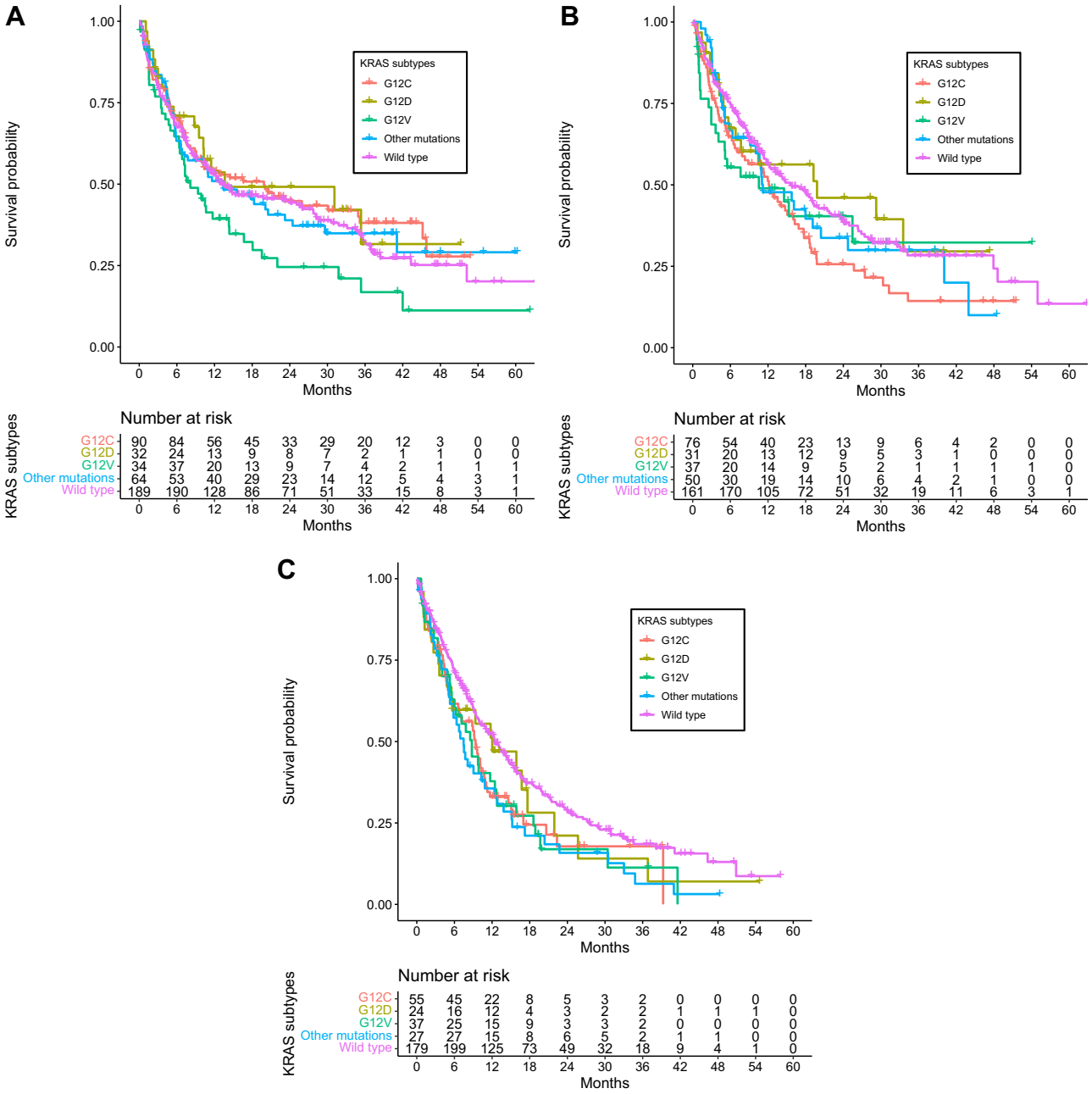


**Figure 1.** Overall survival by *KRAS*m and subtype, (*A*) PD-L1 50% or higher, (*B*) PD-L1 1% to 49%, (*C*) PD-L1 less than 1%. *KRAS*m, *KRAS* mutation; PD-L1, programmed death-ligand 1.

including age, race, performance status, histologic type, and ICI treatment type, were similar across *KRAS*wt and mutation subtypes, both in the total cohort (Table 1) and the PDL1 ≥50% cohort (Supplemental Table 1). Female sex was more common in *KRAS*m (57.8%) than *KRAS*wt (44.4%, $p < 0.001$). Smoking history was more common

**Table 2.** Median Overall Survival, Months (95% CI) by PD-L1 and *KRAS* Status

| PD-L1 Level | *KRAS* Wild Type | *KRAS* G12C | *KRAS* G12V | *KRAS* G12D | *KRAS* Other Mutant |
|---|---|---|---|---|---|
| PD-L1 < 1% | 12.4 (10.1-14.9) | 9.4 (6.8-11.1) | 8.8 (5.6-12.8) | 12.0 (5.5-25.7) | 7.5 (5.2-12.8) |
| PD-L1 1%-49% | 15.8 (12.2-21.5) | 12.2 (7.9-16.9) | 10.5 (4.1-NE) | 19.8 (6.8-NE) | 11.2 (9.2-24.7) |
| PD-L1 ≥ 50% | 13.3 (10.7-25.6) | 19.9 (9.3-35.2) | 8.2 (6.4-16.7) | 13.6 (9.5-NE) | 13.4 (6.8-29.6) |

CI, confidence interval; NE, not estimable; PD-L1, programmed death-ligand 1.

**Table 3.** Adjusted Multivariable HRs (Pairwise Comparisons With *KRAS* G12V), PD-L1 50% and Higher Subgroup

| Adjusted Pairwise Comparison[a] | HR for OS | *p* Value |
|---|---|---|
| *KRAS* G12V vs. *KRAS*wt | 1.63 | 0.008 |
| *KRAS* G12V vs. G12C | 1.78 | 0.004 |
| *KRAS* G12V vs. G12D | 1.78 | 0.046 |
| *KRAS* G12V vs. other *KRAS*m | 1.53 | 0.045 |

[a]Adjusted for age, sex, race, year of diagnosis, histologic type, smoking history, ECOG PS, academic versus community treatment center, treatment type, and commutations (STK11, KEAP1, TP53).
ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; *KRAS*m, *KRAS* mutation; *KRAS*wt, *KRAS* wild type; OS, overall survival; PD-L1, programmed death-ligand 1.

in *KRAS*m (95.3%) than *KRAS*wt (87.9%, $p < 0.001$), and as previously reported, *KRAS* G12D had a lower smoking rate (86.6%).[4,8] PDL1 of 50% or higher was more common in *KRAS*m than *KRAS*wt (42.4% versus 35.3%, $p = 0.001$). Serine/threonine kinase 11 mutations were more common in *KRAS*m (28.5%) than *KRAS*wt (18.6%, $p < 0.001$), whereas TP53 mutations were more common in *KRAS*wt (71.1%) than *KRAS*m (48.5%, $p < 0.001$).

In the PD-L1 50% and higher subgroup, patients with *KRAS* G12V had worse survival (median OS [mOS] = 8.2 mo) compared with *KRAS*wt (mOS = 13.3 mo) and other *KRAS* subgroups (G12C mOS = 19.9 mo, G12D mOS = 13.6 mo, other *KRAS*m mOS = 13.4 mo) (Fig. 1*A* and Table 2). This finding was also significant on adjusted Cox multivariable regression, with hazard ratio [HR] for death for *KRAS* G12V ranging from 1.53-1.78 compared with *KRAS*wt and other *KRAS*m subtypes (all $p < 0.05$; Table 3). Full adjusted multivariable regression results for the PD-L1 50% and higher subgroup are shown in Table 4; in addition to *KRAS* G12V, which was associated with HR for death of 1.63 (95% confidence interval: 1.14–2.33) compared with *KRAS*wt, other factors associated with worse survival included male sex (HR = 1.29), Eastern Cooperative Oncology Group performance status of 2 or higher (HR = 1.82), and *STK11* commutation (HR = 1.46).

In the PD-L1 1% to 49% subgroup, *KRAS*wt and all *KRAS*m subtypes had similar survival (Fig. 1*B* and Table 2). Among patients with PD-L1 less than 1%, all *KRAS*m subtypes had numerically worse survival than *KRAS*wt (Fig. 1*C* and Table 2), as reported in our prior study.[2]

Notably, fewer than 10 patients in the *KRAS* G12C subset received a *KRAS* G12C targeted agent (sotorasib or adagrasib) in any line of therapy, and were deemed unlikely to bias results; sensitivity analyses excluding these patients yielded virtually unchanged results.

## Discussion

In this U.S. clinicogenomic database study of one of the largest cohorts to date of patients with *KRAS*m

**Table 4.** Cox Multivariable Regression for Overall Survival, PD-L1 Higher Than 50% Subgroup (N = 594)

| Characteristic | HR for Death | 95% CI (Lower) | 95% CI (Upper) | *p* Value |
|---|---|---|---|---|
| *KRAS* status (ref: wild type) | | | | |
| G12Cm | 0.91 | 0.68 | 1.23 | 0.553 |
| G12Dm | 0.92 | 0.56 | 1.51 | 0.73 |
| G12Vm | 1.63 | 1.14 | 2.33 | 0.008 |
| Other *KRAS*m | 1.06 | 0.77 | 1.46 | 0.717 |
| Age at diagnosis | 1.01 | 1 | 1.02 | 0.052 |
| Male (ref: female) | 1.29 | 1.03 | 1.62 | 0.025 |
| Race (ref: White) | | | | |
| Black/African American | 0.88 | 0.56 | 1.39 | 0.595 |
| Other/unknown | 1.33 | 1.02 | 1.73 | 0.036 |
| Year of diagnosis (ref: 2016-2017) | | | | |
| 2018-2019 | 1.52 | 1.18 | 1.97 | 0.001 |
| 2020-2021 | 1.78 | 1.23 | 2.56 | 0.002 |
| Non-adenocarcinoma (NSCLC NOS, ref: adenocarcinoma) | 1.54 | 1.03 | 2.3 | 0.036 |
| No history of smoking (ref: former or current smoker) | 1.01 | 0.65 | 1.56 | 0.959 |
| ECOG performance status (ref: 0-1) | | | | |
| ≥2 | 1.82 | 1.36 | 2.42 | <0.001 |
| Missing/unknown | 0.97 | 0.7 | 1.35 | 0.857 |
| Treatment type (ref: anti-PD-L1 monotherapy) | | | | |
| Anti-PD-L1+ anti-CTLA-4 | 2.58 | 0.93 | 7.14 | 0.067 |
| Chemoimmunotherapy | 0.93 | 0.74 | 1.17 | 0.538 |
| Community practice (ref: academic) | 0.69 | 0.46 | 1.03 | 0.068 |
| STK11 commutation | 1.46 | 1.05 | 2.02 | 0.024 |
| KEAP1 commutation | 1.08 | 0.8 | 1.45 | 0.614 |
| TP53 commutation | 1.17 | 0.92 | 1.49 | 0.188 |

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; *KRAS*m, *KRAS* mutation; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; ref, reference.

mNSCLC treated with ICI-based therapy, the association between *KRAS*m and survival differed by *KRAS*m subtype. Although patients with PD-L1 of 50% or higher with *KRAS* G12C, G12D, and other *KRAS*m subtypes exhibited similar survival to those with *KRAS*wt tumors, *KRAS* G12V was associated with significantly worse survival than *KRAS*wt and other *KRAS*m subtypes, on both unadjusted and adjusted analysis accounting for key prognostic baseline covariates. Importantly, this association was not driven by co-alterations in *STK11*, *KEAP1*, or *TP53*, which were seen at similar or lower prevalences in *KRAS* G12V compared with other subtypes, or by higher use of ICI monotherapy in patients with *KRAS* G12V. This effect by the *KRAS*m subtype was unique to the PD-L1 high population and was not seen in PD-L1 low and negative subgroups.

*KRAS* G12V has been implicated as a negative prognostic and predictive biomarker in colorectal cancer,[13] possibly related to differential regulation of downstream apoptosis inhibition pathways seen in codon 12 alterations.[14] In lung cancer, the transversion mutations *KRAS* G12C and G12V (defined by exchange between a purine and pyrimidine base) are more strongly associated with smoking history compared with the transition mutation *KRAS* G12D (interchange of one purine or pyrimidine for another),[4,15] and may be expected to have better outcomes with immunotherapy. In contrast to a recent clinicogenomic study that found worse outcomes with PD-L1 blockade with *KRAS* G12D compared with other *KRAS*m lung cancers,[8] the *KRAS* G12D subgroup in our study did not exhibit worse survival with ICI therapy compared with *KRAS*wt or other *KRAS*m subtypes, in any PD-L1 subgroup. *KRAS* G12V has previously been shown to correlate with inferior survival outcomes in patients with mNSCLC treated with platinum-based chemotherapy,[16] but this is the first study to report a differential *KRAS* G12V association in a contemporary ICI-treated cohort. The exact mechanistic reasons for this effect, and its specificity to the PD-L1 high cohort, are unknown.

This retrospective study has several limitations. Despite the utilization of a large nationwide clinicogenomic database, the number of patients in each subgroup was limited after stratification by PD-L1 and *KRAS* subtype. As a result, we were not able to separately analyze smaller subgroups of interest including *KRAS* G12A, and G13 subtypes, and also were not able to assess differences with treatment with PD-L1 inhibition alone versus chemoimmunotherapy. Given our focus on a PD-L1-stratified analysis, only patients with known PD-L1 expression were included in our cohort. Residual confounding by exclusion of PD-L1 unknown patients, or other unmeasured factors, cannot be excluded. Finally, mutational subtypes were defined using different solid- and liquid-based Foundation next-generation sequencing profiling test types, which may have resulted in nonuniform capture of mutations leading to misclassification.

Despite these limitations, our results suggest a note of caution in clinical practice: all *KRAS*m should not be regarded as uniform predictors of responsiveness to ICI-based therapy. Even in the PD-L1 high population, *KRAS* G12V in particular may portend worse outcomes with ICI-based therapy, and these patients may benefit from treatment intensification approaches. Further study is needed to validate these findings in larger prospective cohorts and to delineate the mechanistic underpinnings of survival heterogeneity by *KRAS*m subtypes.

## CRediT Authorship Contribution Statement

**Lova Sun:** Conceptualization, Methodology, Investigation, Writing - original draft, Writing - reviewing & editing.

**Yunyun Zhou:** Data curation, Investigation, Software, Validation, Writing - review & editing, Visualization.

**Elizabeth A. Handorf:** Data curation, Investigation, Software, Validation, Writing - review & editing, Visualization.

**Hossein Borhaei:** Conceptualization, Supervision, Writing - review & editing.

**Jessica Bauman:** Conceptualization, Methodology, Supervision, Writing - review & editing.

**Charu Aggarwal:** Conceptualization, Methodology, Supervision, Writing - review & editing.

## Disclosure

Dr. Sun declares advisory board/consulting from Regeneron, GenMab, Seagen, and Bayer; and research support (clinical trials) from Blueprint, Seagen, IO Biotech, Erasca, Immunocore, and Abbvie. Dr. Borghaei declares research support (clinical trials) from Bristol-Myers Squibb, Eli Lilly, Amgen; advisory board/consulting from Bristol-Myers Squibb, Eli Lilly, Genentech, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTEO, Jazz, Janssen, Puma, BerGenBio, Bayer, Iobiotech, Grid Therapeutics; DSMB for University of Pennsylvania: CAR T Program, Takeda, Incyte, Novartis, Springworks; honoraria from Amgen, Pfizer, Daiichi, Regeneron; stock options for Sonnetbio, Inspirna, Nucleai; and travel support from Amgen, Bristol-Myers Squibb, Merck, Eli Lilly, EMD-Serono, Genentech, Regeneron, Mirati. Dr. Bauman declares advisory board/consulting for EMD-Serono and editorial support from Pfizer. Dr. Aggarwal declares

grants from AstraZeneca, Genentech, Incyte, Loxo@Eli Lilly, Macrogenics, Medimmune, and Merck Sharp & Dohme, and personal fees from Genentech, Eli Lilly, Celgene Merck, AstraZeneca, Blueprint Genetics, Shionogi, Daiichi Sankyo/AstraZeneca, Regeneron/Sanofi, Eisai, BeiGene, Turning Point, Pfizer, Janssen, Boehringer Ingelheim. The remaining authors declare no conflict of interest.

## Acknowledgments

This was funded in part by NIH/NCI grant P30CA006927 (Fox Chase Cancer Center Support Grant).

## 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.2024.100755.

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