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KRAS^{G12C} Mutation Is Associated with Increased Risk of Recurrence in Surgically Resected Lung Adenocarcinoma

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Abstract

Purpose: *KRAS*^{G12C} is the most common *KRAS* mutation in primary lung adenocarcinoma (LUAD). Phase I clinical trials have demonstrated encouraging clinical activity of *KRAS*^{G12C} inhibitors in the metastatic setting. We investigated disease-free survival (DFS) and tumor genomic features in patients with surgically resected *KRAS*^{G12C}-mutant LUAD.

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Experimental Design: Patients who underwent resection of stage I-III LUAD and next-generation sequencing (NGS) were evaluated. Exclusion criteria were receipt of induction therapy, incomplete resection, and low-quality NGS. Mutations were classified as *KRAS* wild-type (*KRAS*^{wt}), G12C (*KRAS*^{G12C}), or non-G12C (*KRAS*^{other}). DFS was compared between groups using the log-rank test; factors associated with DFS were assessed using Cox regression. Mutual exclusivity and co-occurrence, tumor clonality, and mutational signatures were assessed.

Results: In total, 604 patients were included: 374 *KRAS*^{wt} (62%), 95 *KRAS*^{G12C} (16%), and 135 *KRAS*^{other} (22%). Three-year DFS was not different between *KRAS*-mutant and *KRAS*^{wt} tumors. However, 3-year DFS was worse in patients with *KRAS*^{G12C} than *KRAS*^{other} tumors (log-rank p=0.029). *KRAS*^{G12C} tumors had more lymphovascular invasion (51% vs. 37%; p=0.032) and higher tumor mutation burden (median [interquartile range], 7.0 [5.3–10.8] vs. 6.1 [3.5–9.7]; p=0.021), compared with *KRAS*^{other} tumors. *KRAS*^{G12C} mutation was independently associated with worse DFS on multivariable analysis. Our DFS findings were externally validated in an independent The Cancer Genome Atlas cohort.

Conclusions: *KRAS*^{G12C} mutations are associated with worse DFS after complete resection of stage I-III LUAD. These tumors harbor more-aggressive clinicopathologic and genomic features than other *KRAS*-mutant tumors. We identify a high-risk group for whom *KRAS*^{G12C} inhibitors may be investigated to improve survival.

Keywords

KRAS; G12C; lung adenocarcinoma; surgery; disease-free survival

Introduction

The *KRAS* gene encodes an oncoprotein involved in key signaling pathways for tumor growth and differentiation and is the most frequently mutated oncogene in all cancer types (1). Somatic mutations in *KRAS* are found in 25% to 33% of primary lung adenocarcinoma (LUAD) (2,3). In stage IV LUAD, patients with *KRAS*-mutant primary tumors have demonstrated poor overall survival (4) and less clinical benefit from standard-of-care systemic therapies, compared with *KRAS*^{wt} tumors (5).

During the last few decades, the KRAS protein has been viewed as undruggable, owing to the lack of deep pockets for direct small-molecule-inhibitor binding. Consequently, efforts to develop targeted therapies for *KRAS*-mutant tumors have focused on inhibition of downstream effector proteins in the MAPK pathway, such as BRAF, MEK, and ERK. However, inhibition of these downstream targets is often accompanied by on-target, nontumor toxicities, due to the inhibition of this signaling pathway in normal cells (6,7). As a result, this narrow therapeutic index has precluded the successful clinical development of agents targeting *KRAS* (5,8).

The majority of *KRAS* mutations in LUAD are single-base substitutions (SBSs) in codons 12 or 13—the most common being G12C, which occurs in 13% to 16% of LUAD (3,9). The recent discovery of direct *KRAS*^{G12C} inhibition by use of a trapping mechanism has led to promising preclinical and early-phase drug development (1,10–12). For example, in two

phase I clinical trials of sotorasib and adagrasib (NCT03600883 and NCT03785249), encouraging clinical activity has been observed in patients with non-small cell lung cancer (NSCLC) (13–15).

Given the encouraging early results in the development of *KRAS*^{G12C} inhibitors, a greater understanding of the genomic complexity of *KRAS*^{G12C}-mutant tumors and the oncologic outcomes of patients with these tumors is needed, especially in the setting of curative-intent surgery for earlier-stage disease (16,17). To address this knowledge gap, we investigated and compared tumor genomic features and disease-free survival (DFS) in patients with surgically resected LUAD harboring mutations in *KRAS*^{G12C}, compared to *KRAS*^{other} and *KRAS*^{wt} tumors. The results of our study offer insight into the potential impact that *KRAS*^{G12C} inhibitors may have in patients with early-stage LUAD who undergo surgery as their first treatment.

Materials and Methods

Study Population and Data Collection

Following institutional review board approval at Memorial Sloan Kettering Cancer Center, patients who underwent complete (R0) surgical resection for pathologic stage I-III LUAD from February 2010 to December 2018 and had targeted next-generation sequencing (NGS; MSK-IMPACT) (18) performed on the primary tumor were identified. All patients provided written informed consent to participate in the institutional review board–approved protocol, and all studies were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Exclusion criteria were as follows: receipt of induction therapy, microscopic (R1) or macroscopic (R2) residual disease, and low-quality NGS (see CONSORT diagram, Supplementary Figure 1). Tumors were classified according to primary tumor *KRAS* mutation status as either wild-type (*KRAS*^{wt}), *KRAS*(G12C) mutation (*KRAS*^{G12C}), or other *KRAS* mutation (*KRAS*^{other}).

Prospectively collected demographic, imaging, staging (American Joint Committee on Cancer 8th edition), pathologic, genomic, recurrence, and follow-up data were reviewed. Predominant invasive LUAD histologic subtypes were classified as either lepidic, acinar, papillary, micropapillary, or solid (19). Follow-up was performed in accordance with National Comprehensive Cancer Network guidelines (20). Metachronous lesions were distinguished from recurrences using Martini and Melamed criteria (21), with confirmation of clonal relatedness using genomic data, as previously reported by our group (22).

MSK-IMPACT Sequencing

Tumor genomic profiling was performed and analyzed as previously described (18). The sequencing breadth of the IMPACT panel has increased over time, resulting in 8, 190, and 406 patients sequenced with 341-, 410-, and 468-gene panels, respectively. Tumor mutation burden (TMB) was defined as the total number of nonsynonymous single-nucleotide insertion or deletion mutations per megabase and was normalized by panel size by dividing the total number of mutations by the length of the coding region captured by each panel (0.98, 1.06, and 1.22 Mb in the 341-, 410-, and 468-gene panels, respectively). Fraction of

genome altered (FGA) was computed from the output of the FACETS (Fraction and Allele-specific Copy number Estimates from Tumor Sequencing) algorithm, which provides accurate, purity- and ploidy-corrected, integer DNA copy number calls from sequenced samples (23). FGA is defined as the fraction of the genome that differs from the major integer copy number, which represents the integer total copy number spanning the largest portion of the genome.

Statistical and Genomic Data Analysis

The primary endpoint—DFS—was defined as the time from surgery to first recurrence or death from any cause; patients were otherwise censored at the time of last follow-up. DFS was estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Median follow-up was estimated using the reverse Kaplan-Meier method. Patterns of recurrence were assessed using the cumulative incidence of locoregional recurrence (CIR-LR) and distant recurrence (CIR-DR) in the $KRAS^{G12C}$ and $KRAS^{other}$ groups. Patients with both locoregional and distant recurrence were included in the distant recurrence analysis. Clinicopathologic and genomic variables (including specific genes, pathways, TMB, and FGA) were compared between groups using Fisher's exact test for categorical factors and the Wilcoxon rank-sum test for continuous factors. A total of two Cox regression models were used to quantify the association between clinicopathologic or genomic factors and DFS—(1) within the overall cohort and (2) within only the $KRAS^{G12C}$ group—using hazard ratios (HRs) and 95% confidence intervals (CIs). Both regression analyses used identical lists of variables, with the exception of the *KRAS*-mutation group, which was included in only the Cox regression for the overall cohort. Multivariable models for all factors were adjusted for pathologic stage. To quantify the associations between specific genes and DFS, an additional univariable analysis was performed using all genes with an alteration frequency >8% after false-discovery rate (FDR) correction.

Analysis of specific somatic alterations was performed using OncoKB (24) to remove variants of unknown significance. For the analysis of co-occurrence and mutual exclusivity, we assessed all genes known to be drivers in LUAD (24). In total, 121 genes were identified at the intersection of the *a priori* pathway templates and the MSK-IMPACT panel. A pathway was considered to be altered in a tumor if at least one gene within the corresponding pathway template was altered. Mutual exclusivity and co-occurrence of alterations in genes and oncogenic cell signaling pathways were assessed using Fisher's exact test, and *p* values were adjusted to correct for multiple comparisons using FDR correction.

Differences in primary tumor clonality were investigated between groups using the cancer cell fraction, as calculated by FACETS. Clonality assessment was able to be performed on 72 patients in the $KRAS^{G12C}$ group and 95 patients in the $KRAS^{other}$ group. Primary tumor clonality was defined as a cancer cell fraction >0.8, as in prior reports (25,26). Variant allele frequency is the fraction of sequence reads that contain a specific DNA variant, divided by the overall coverage at that locus.

Mutational signatures were computed using the most recent version of the SBS signatures defined in the Catalogue of Somatic Mutations in Cancer database for somatic mutation

signature analysis (27). Tumors with ≥13.8 mutations/Mb were evaluated for the *KRAS*^{G12C} (n=67) and *KRAS*^{other} (n=83) groups, in accordance with the previously published threshold (28). Tumors were considered to have a detectable signature if the mean signature value was >0.1, as previously described (27).

Analyses were conducted using Stata 15.0 (StataCorp, College Station, TX) and R 3.5.1 (R Core Team, Vienna, Austria). Statistical tests were two-sided, and $p<0.05$ was considered statistically significant.

External Validation

External validation of the relationship between *KRAS*^{G12C} mutation and DFS was performed using The Cancer Genome Atlas (TCGA) LUAD data set (N=476) (20). Patients with pathologic stage I-III LUAD who did not receive induction therapy were included. Tumors were classified according to *KRAS*-mutation status. DFS was estimated using the Kaplan-Meier method and was compared between groups using the log-rank test.

Results

Clinicopathologic Characteristics

A total of 604 patients met the inclusion criteria (Table 1). *KRAS* mutation status was as follows: 374 *KRAS*^{wt} (62%), 95 *KRAS*^{G12C} (16%), and 135 *KRAS*^{other} (22%). The median age at resection was 68 years (interquartile range [IQR], 62–74), and two-thirds of patients were women (n=402 [67%]). Most patients (77%) had a history of smoking, with a median of 27 pack-years (IQR, 15–45). Patients with *KRAS*-mutant LUAD were more commonly smokers, compared with *KRAS*^{wt} LUAD. Sublobar resection was performed in 214 patients (35%). A majority of patients had pathologic stage I LUAD (n=447 [74%]); 95 patients (16%) had stage II LUAD, and 62 patients (10%) had stage III LUAD. Of note, patients with *KRAS*^{G12C} and *KRAS*^{other} tumors were more likely to have high (≥50%) programmed death-ligand 1 (PD-L1) expression (n=35/95 [37%] and n=47/135 [35%], respectively), compared with patients with *KRAS*^{wt} tumors (n=94/374 [25%]) (p=0.013). Adjuvant therapy was administered to 116 patients (19%) and was not statistically significantly different between groups. Regimens included chemotherapy only (n=95 [82%]), chemoradiation (n=18 [16%]), radiotherapy only (n=2 [1.7%]), and immunotherapy (n=1 [0.8%]). Median follow-up was 2.51 years (IQR, 1.74–3.30).

KRAS *Mutation Status, Recurrence Patterns, and Survival*

The specific types of *KRAS* alterations and associated frequencies are listed in Supplementary Table 1. The *KRAS*^{other} group predominantly comprised patients with G12D (n=33/135 [24%]), G12V (n=32/135 [24%]), and G12A (n=23/135 [17%]) mutations. Three-year DFS for the overall cohort was 73.6% (95% CI, 69.5%−78.0%). DFS was not statistically significant different between patients with any *KRAS* mutation (3-year DFS, 75.3% [95% CI, 69.2%−82.0%]) and patients with *KRAS*^{wt} LUAD (3-year DFS, 72.5% [95% CI, 67.1%−78.3%]), with a hazard ratio (HR) of 0.95 (95% CI, 0.68–1.34) (p=0.785; Figure 1A). However, among patients with *KRAS*-mutant tumors (n=230), DFS was substantially worse for patients with *KRAS*^{G12C} mutations (3-year DFS, 68.7% [95% CI,

58.9%−80.3%]) than for those with *KRAS*^{other} mutations (3-year DFS, 80.0% [95% CI, 72.4%−88.3%]), with an HR of 1.82 (95% CI, 1.06–3.15) (p=0.029; Figure 1B).

The CIR-LR was higher in the *KRAS*^{G12C} group (3-year CIR-LR, 8.0% [95% CI, 2.8% −16.8%]) than in the *KRAS*^{other} group (3-year CIR-LR, 2.3% [95% CI, 0.6%−6.1%) but did not reach statistical significance (Gray's p=0.119; Supplementary Figure 2A). The subtle observation of higher CIR-LR appeared to occur past the 2-year mark after surgery. Similarly, the CIR-DR was higher in the *KRAS*^{G12C} group (3-year CIR-DR, 20.8% [95% CI, 12.6%−30.4%]) than in the *KRAS*^{other} group (3-year CIR-DR, 13.0% [95% CI, 7.2% −20.7%]) but again did not reach statistical significance (Gray's p=0.070; Supplementary Figure 2B). The observed divergence, however, appeared to occur earlier in the follow-up period. Overall, at 3 years after surgery, the CIR-DR was more than double the CIR-LR across both groups.

Clinicopathologic Factors Associated with DFS

On univariable analysis (N=604), the following factors were associated with DFS: diffusing capacity of the lungs for carbon monoxide (DLCO), primary tumor maximum standardized uptake value, open (thoracotomy) resection, pathologic tumor size, lymphovascular invasion (LVI), visceral pleural invasion (VPI), spread through air spaces (STAS), micropapillary or solid histologic subtype, pathologic node positivity, pathologic stage II or III LUAD, *KRAS*^{G12C} mutation, TMB, and FGA (p<0.1; Supplementary Table 2). On multivariable analysis, after adjustment for pathologic stage, *KRAS*^{G12C} mutation was independently associated with worse DFS (HR, 1.84 [95% CI, 1.01–3.36]; p=0.046) (Table 2). In addition, DLCO (HR, 0.99 [95% CI, 0.98–1.00]; p=0.031), LVI (HR, 2.36 [95% CI, 1.43–3.91]; p=0.001), VPI (HR, 1.66 [95% CI, 1.10–2.51]; p=0.015), STAS (HR, 1.81 [95% CI, 1.02–3.23]; p=0.044), and pathologic stage II or III (vs. stage I; HR, 1.80 [95% CI, 1.18–2.76]; p=0.007) were also independently associated with worse DFS.

Factors prognostic for DFS were then investigated within the *KRAS*^{G12C} group (n=95). On univariable analysis, age at resection, pack-years, DLCO, primary tumor maximum standardized uptake value, primary tumor size, LVI, VPI, STAS, micropapillary or solid subtype, pathologic node positivity, pathologic stage II or III, and TMB were associated with DFS (p<0.1; Supplementary Table 3). On multivariable analysis, primary tumor LVI (HR, 9.57 [95% CI, 2.20–41.54]; p=0.003) and VPI (HR, 2.25 [95% CI, 1.03–4.94]; p=0.042) were independently associated with DFS (Table 2).

Clinicopathologic and Genomic Differences Between Patients with KRAS^{G12C} and KRAS^{other} Tumors

Clinicopathologic and genomic factors were then compared between patients with *KRAS*^{G12C} and KRAS^{other} tumors (Figure 2). LVI (51% vs. 37%; p=0.032) and pathologic lymph node metastasis (21% vs. 12%; p=0.059) were more common in the *KRAS*^{G12C} group. *KRAS*^{G12C} tumors were also found to have higher TMB (median [IQR], 7.0 [5.3–10.8] vs. 6.1 [3.5–9.7]; p=0.021) and FGA (x100; median [IQR], 3.8 [0.4–8.9] vs. 1.5 [0.2–7.3]; p=0.053).

The ten most commonly altered genes were compared between groups (Figure 2). Although no differences reached statistical significance, *KRAS*^{G12C} tumors had more *STK11* and *NF1* mutations than *KRAS*^{other} tumors. Conversely, *KRAS*^{other} tumors were nearly twice as likely to have a truncating mutation in *RBM10*, an RNA-binding protein and splicing regulator (29).

Genes Associated with DFS

To determine whether the differences in alteration frequencies described above were also prognostic for DFS, an additional univariable analysis was performed using the same list of genes (Supplementary Table 4). In the overall cohort, two genes (*TP53*: HR, 1.65 [95% CI, 1.18–2.31]; Q=0.024; and *RBM10*: HR, 0.43 [95% CI, 0.22–0.84]; Q=0.024) were associated with DFS after FDR correction, a finding that was previously reported by our group (30). In the *KRAS*^{G12C} group, no genes were statistically significantly associated with DFS after FDR correction.

Mutual Exclusivity and Co-occurrence Patterns

Mutual exclusivity and co-occurrence patterns of individual genes and oncogenic pathways were then explored between groups. In the overall cohort, *STK11* and *KEAP1* were significantly co-occurrent, as previously described (31), whereas any *KRAS* mutation was predictably mutually exclusive with other RAS pathway genes (e.g., *EGFR*, *BRAF*, *MET*) (FDR-p<0.05; Supplementary Figure 3A). Interestingly, no genes were found to be statistically significantly co-occurrent with *KRAS*^{G12C} mutation or *KRAS*^{other} mutation. Among *KRAS*^{G12C} tumors, *TP53* and *NF1* mutations were observed to be significantly co-occurrent (p=0.03; Supplementary Figure 3B). Finally, among *KRAS*^{other} tumors, *STK11* and *KEAP1* were again found to statistically significantly co-occur (p=0.007; Supplementary Figure 3C).

Clonality Patterns and Somatic Mutation Signatures of KRAS^{G12C} and KRAS^{other} Tumors

Next, differences in primary tumor clonality were explored between the *KRAS*^{G12C} and *KRAS*^{other} groups. *KRAS* mutation was found to be a clonal event in 90% of *KRAS*^{G12C} tumors (n=65/72) and 91% (n=86/95) of *KRAS*^{other} tumors (Supplementary Figure 4). This confirms that *KRAS* mutations are an early, truncal alteration in the evolution of LUAD tumors.

Detectable somatic mutation signatures were then investigated between the *KRAS*^{G12C} and *KRAS*^{other} groups (Figure 3). Overall, the smoking signature (SBS4) was most commonly detectable in both groups (33% vs. 42%, respectively; p=0.24). Interestingly, *KRAS*^{G12C} tumors had a statistically significantly higher prevalence of the SBS2 signature (attributed to APOBEC activity(27)), compared with *KRAS*^{other} tumors (16% vs. 6%; p=0.04). Conversely, *KRAS*^{other} tumors had higher rates of SBS16 (17% vs. 6%; p=0.041) and SBS18 (10% vs. 2%; p=0.043), compared with *KRAS*^{G12C} tumors.

External Validation of DFS Association

To externally validate our findings, we queried a TCGA data set for all patients with pathologic stage I-III LUAD who did not undergo induction therapy; a total of 476 patients

were identified. *KRAS* mutation status was as follows: 323 $KRAS^{wt}$ (68%), 63 $KRAS^{G12C}$ (13%), and 90 $KRAS^{other}$ (19%) (Supplementary Table 5). No difference was noted in 3-year DFS between patients with any *KRAS* mutation and patients with $KRAS^{wt}$ LUAD (HR, 1.18 [95% CI, 0.89–1.56]; p=0.244; Figure 4A). However, among patients with *KRAS*-mutant tumors (n=153), patients with $KRAS^{G12C}$ mutation were again found to have significantly worse 3-year DFS than patients with $KRAS^{other}$ mutation (31.3% versus 54.2%, respectively; HR, 1.88 [95% CI, 1.18–3.00]; p=0.007; Figure 4B), confirming the relationship between $KRAS^{G12C}$ mutation and DFS in our study.

Discussion

The recent development of $KRAS^{G12C}$ inhibitors and their promising early results in phase I clinical trials have necessitated the genomic characterization and examination of long-term oncologic outcomes in patients with surgically resected $KRAS^{G12C}$-mutant tumors. We have shown that, compared with $KRAS^{other}$ mutations, $KRAS^{G12C}$ primary tumor mutations portended worse DFS in both our institutional data set as well as an external TCGA data set. $KRAS^{G12C}$ mutation was also independently associated with worse DFS in our cohort. $KRAS^{G12C}$ tumors appeared to contain a greater proportion of aggressive pathologic features (LVI, positive lymph nodes) and genomic perturbations (higher TMB and FGA) than $KRAS^{other}$ tumors. Through extensive genomic characterization, we discovered that no common oncogenes or tumor suppressors were co-occurrent or mutually exclusive with $KRAS^{G12C}$ tumors. However, in the overall cohort, *STK11* and *KEAP1* were significantly co-occurrent, a finding supported by studies in the metastatic setting (32). Finally, we have shown that the vast majority of both $KRAS^{G12C}$ and $KRAS^{other}$ tumors harbor clonal populations of *KRAS*-mutant cells, confirming that acquisition of this alteration is an early event in the mutagenesis of these tumors.

KRAS somatic mutations have been shown to be associated with decreased survival in prior studies, with 5-year overall survival ranging from 22% to 30% in patients with *KRAS*-mutant NSCLC (4,32). Although this association with poor prognosis is well documented for advanced disease, the influence of *KRAS* mutation on survival in patients with early-stage disease remains poorly characterized. In a smaller series (N=179), Nadal and colleagues found overall *KRAS* mutation was associated with worse DFS (log-rank p=0.006) and overall survival (log-rank p=0.046) (17). However, this cohort included all stages of LUAD, with 20% of *KRAS*-mutant tumors (n=21) being stage III or IV in this study. When the analysis was repeated for only patients with stage I disease (n=121), the survival difference substantially diminished (log-rank p=0.049). In the two larger, early-stage cohorts in our study (study cohort, N=604; TCGA external validation cohort, N=476), 3-year DFS was not statistically significantly different between patients with *KRAS*-mutant and $KRAS^{wt}$ tumors, indicating there was no prognostic significance for the overall *KRAS* mutation population.

Targeting $KRAS^{G12C}$—the most prevalent of the *KRAS* alterations, present in up to half of *KRAS*-mutant tumors (33)—has led to encouraging tumor responses in phase I clinical trials (13,34). In the Nadal study, the 2-year DFS for patients with $KRAS^{G12C}$ tumors was 42.9%, compared with approximately 65.0% for patients with other *KRAS*-mutant tumors.

However, the *KRAS*^{G12C} group comprised only 35 patients, with an unreported stage distribution. In the present study, 3-year DFS for patients with *KRAS*^{G12C} tumors was also substantially worse than that for patients with *KRAS*^{other} tumors in our institutional cohort (68.7% vs 80.0%, respectively). Additionally, analysis of the TCGA database yielded similar results, with a 3-year DFS of 31.3% versus 54.2%, respectively, in this external validation cohort. Interestingly, the observed survival differences do not appear to be linked to comutation patterns, as no genes were significantly co-occurrent with *KRAS*^{G12C} alteration on genomic analysis, and likewise no other genes were prognostic for DFS within this group. One possible explanation for this survival detriment may involve the lack of immunogenicity in *KRAS*^{G12C} tumors. A recent study by Aredo and colleagues found that these tumors were significantly associated with low (1%−49%) PD-L1 expression (35). In the present study, *KRAS*^{G12C}-mutant tumors with high PD-L1 expression (≥50%)—although these were in the minority—were significantly more common in the *KRAS*^{G12C} group than in the *KRAS*^{wt} group (37% vs. 23%; p=0.013). On the basis of preclinical data, *KRAS*^{G12C} inhibitors enhance antitumor immunity, which may be helpful for eradicating micrometastatic disease (9). The ability to target this alteration in a newly defined high-risk population—whether in the adjuvant or neoadjuvant setting—has major therapeutic implications.

Numerous studies have shown that *KRAS* mutation is an early event in lung tumorigenesis (36–38). In a recent analysis of NSCLC tumor evolution, primary tumors with alterations in any of four genes (*TP53*, *KEAP1*, *STK11*, and *EGFR*) were shown to have a higher proportion of clonal tumor cell populations, signifying that these genes play a role in tumor initiation (36). In a separate study involving multi-region sequencing, *KRAS* mutations were present in both minimally invasive adenocarcinoma or adenocarcinoma in situ and paired invasive LUAD, suggesting that *KRAS* mutation is an early mutagenic event and an indicator of malignant transition (37). Furthermore, in the landmark TRACERx NSCLC tumor evolution study, 88% of samples with *KRAS* mutations were deemed to be clonal populations (38). In our study, 90% of overall *KRAS*-mutant tumors, as well as 90% of *KRAS*^{G12C}-mutant tumors, were found to harbor clonal cancer cell populations. This knowledge, coupled with the increased risk of recurrence in patients with *KRAS*^{G12C} tumors in this study, provides encouraging evidence to support the use of *KRAS*^{G12C} inhibitors for preventing or delaying tumor relapse in patients with early-stage LUAD.

Recent large-scale analyses have identified numerous somatic mutational signatures across the spectrum of cancer types (27). Although somatic mutational signature analysis most commonly relies on whole-genome or whole-exome sequencing data, our group has previously shown the feasibility of using MSK-IMPACT (28). In the present study, *KRAS*^{G12C} tumors were associated with high activity of the putative APOBEC mutational signature (SBS2), whereas *KRAS*^{other} tumors were associated with the putative reactive oxygen species signature (SBS18). Loss-of-function alterations in APOBEC-related genes lead to DNA hypermutation and inaccurate RNA editing and are associated with tumorigenesis as well as drug resistance (19,39,40). Furthermore, a recent analysis of immune-response-related mutational signatures in NSCLC showed that high TMB combined with APOBEC-related mutational signatures was predictive of response to immunotherapy

(41), revealing an intriguing new patient population that may derive benefit from these agents.

Limitations of our study include a low number of death events in our early-stage cohort such that overall survival was unable to be explored as an outcome. Another limitation is that our findings require further validation from international data sets such as those from Asia, where the incidence of *KRAS* mutations in LUAD is lower, which would provide useful information regarding the implications of $KRAS^{G12C}$ mutation and inhibition in a geographically diverse population. Despite these limitations, this externally validated analysis from the largest data set of patients with resected $KRAS^{G12C}$ LUAD provides evidence to support the investigation of sotorasib, adagrasib (MRTX849), or other $KRAS^{G12C}$ inhibitors in the adjuvant setting, with the goal of improving DFS.

Mutations in $KRAS^{G12C}$ are the most common *KRAS* mutations in lung cancer and are independently prognostic for poor DFS after complete resection of stage I-III LUAD. We have shown that the vast majority of $KRAS^{G12C}$ tumors harbor clonal populations of $KRAS^{G12C}$-mutant cells, and these tumors appear to harbor more genomic perturbations and aggressive clinicopathologic features than other *KRAS*-mutant tumors. Additionally, $KRAS^{G12C}$ mutation was not found to be co-occurrent with actionable alterations in other common LUAD driver genes. Our findings provide evidence supporting the investigation of $KRAS^{G12C}$ inhibitors in the adjuvant setting in this vulnerable patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest: Yonina R. Murciano-Goroff has received travel, accommodations, and expenses from AstraZeneca. Sandra Misale consulted for Boehringer-Ingelheim. Matthew J. Bott serves as a consultant for AstraZeneca. Prasad S. Adusumilli has received research funding from ATARA Biotherapeutics and Acea Biosciences, has served on the Scientific Advisory Board or as consultant to ATARA Biotherapeutics, Bayer, Carisma Therapeutics, Imugene, and Takeda Therapeutics, and has patents, royalties, and intellectual property on mesothelin-targeted CARs and other T-cell therapies, method for detection of cancer cells using virus, and pending patent applications on T-cell therapies. Daniela Molena is a consultant for Johnson & Johnson, Urogen, Intuitive, and Boston Scientific. Gaetano Rocco has financial relationships with Scanlan. Rona Yaeger has received research funding from Array BioPharma/Pfizer and Boehringer Ingelheim and has consulted for Array BioPharma/Pfizer, Mirati Therapeutics, and Natera. Gregory J. Riely has received research funding from Novartis, Genentech, Millennium Pharmaceuticals, GlaxoSmithKline, Pfizer, Infinity Pharmaceuticals, ARIAD Pharmaceuticals, has a patent application submitted covering pulsatile use of erlotinib to treat or prevent brain metastases, and has received travel expenses from Merck Sharp & Dohme. James M. Isbell is a consultant for Genentech and has an equity interest in LumaCyte LLC. Bob T. Li has served as an uncompensated advisor and consultant to Amgen, Genentech, Boehringer Ingelheim, Lilly, AstraZeneca, Daiichi Sankyo, and has received consulting fees from Guardant Health and Hengrui Therapeutics. He has received research grants to his institution from Amgen, Genentech, AstraZeneca, Daiichi Sankyo, Lilly, Illumina, GRAIL, Guardant Health, Hengrui Therapeutics, MORE

Health and Bolt Therapeutics. He has received academic travel support from Resolution Bioscience, MORE Health, and Jiangsu Hengrui Medicine. He is an inventor on two institutional patents at MSK and has intellectual property rights as a book author at Karger Publishers. David R. Jones serves as a consultant for AstraZeneca and on a Clinical Trial Steering Committee for Merck. All other authors have no potential conflicts to disclose.

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Statement of Translational Relevance:

KRAS^{G12C} is the most prevalent of the *KRAS* alterations in primary lung adenocarcinoma (LUAD), present in up to half of cases. The association between *KRAS* somatic mutations and decreased survival is well-documented in metastatic LUAD. However, the influence of *KRAS* mutation on survival in early-stage disease remains poorly characterized. The recent development of KRAS^{G12C} inhibitors and their promising early results in phase I clinical trials necessitates the genomic characterization and examination of long-term oncologic outcomes in patients with surgically resected *KRAS*^{G12C}-mutant tumors. We have shown that, compared with *KRAS*^{other} mutations, *KRAS*^{G12C} primary tumor mutations portended worse disease-free survival in both our institutional data set and an external TCGA data set. *KRAS*^{G12C} tumors contain a greater proportion of aggressive pathologic features (LVI, positive lymph nodes) and genomic perturbations (higher TMB and FGA) than *KRAS*^{other} tumors. We identify a high-risk group for whom *KRAS*^{G12C} inhibitors may be investigated to improve survival.

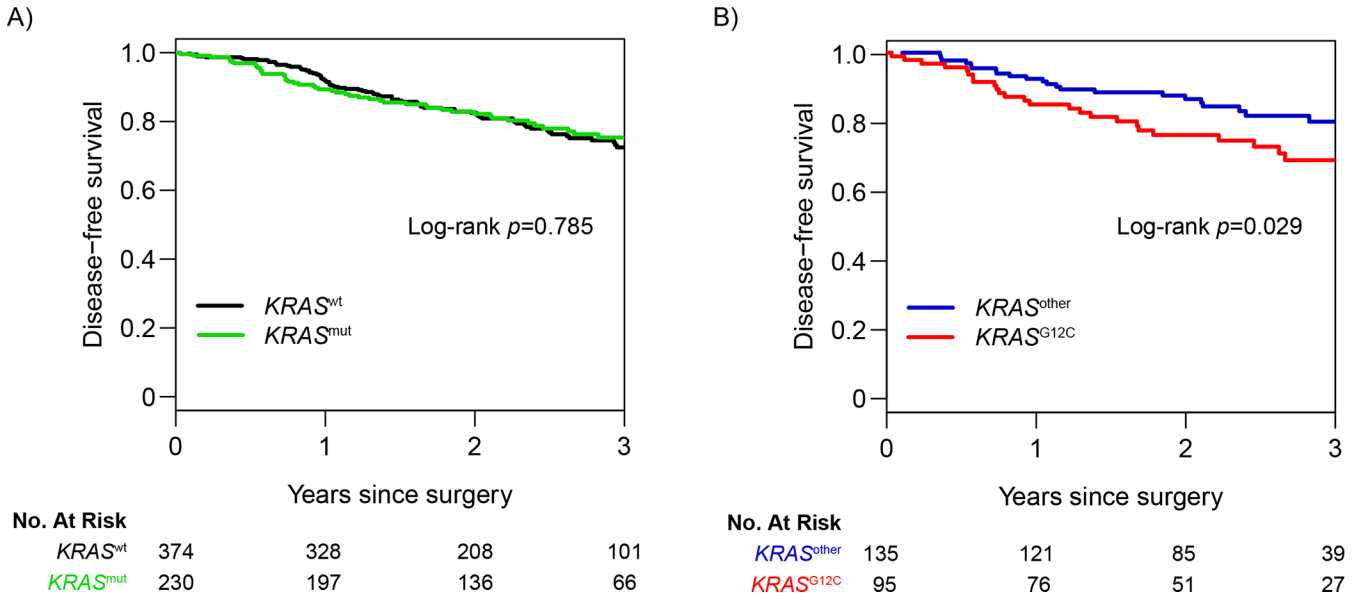


Figure 1. Association between *KRAS* mutation status and disease-free survival in the study cohort (N=604).

Three-year disease-free survival for (A) all *KRAS*-mutant (*KRAS*^{mut}) tumors versus *KRAS* wild-type (*KRAS*^{wt}) tumors and for (B) *KRAS*^{G12C} tumors versus all other *KRAS*-mutant tumors (*KRAS*^{other}).

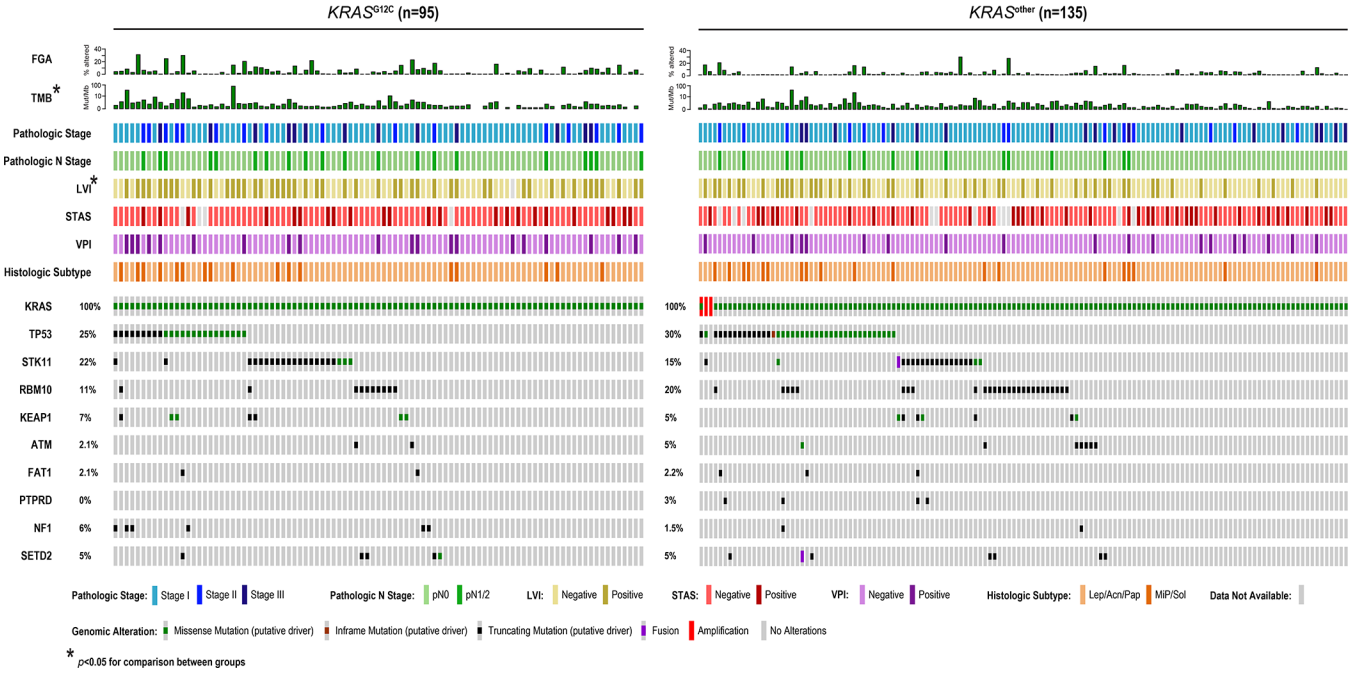


Figure 2. Clinicopathologic and genomic features of *KRAS*-mutant tumors.

Comparison of clinicopathologic variables, genomic factors, and specific genes between the *KRAS*^{G12C} and other *KRAS* mutation (*KRAS*^{other}) groups. All genes with an alteration frequency >8% are shown. *p<0.05 for comparison between groups using Fisher's exact test for categorical factors and the Wilcoxon rank-sum test for continuous factors. Acn, acinar; FGA, fraction of genome altered; Lep, lepidic; LVI, lymphovascular invasion; MiP, micropapillary; Pap, papillary; Sol, solid; STAS, spread through air spaces; TMB, tumor mutation burden; VPI, visceral pleural invasion.

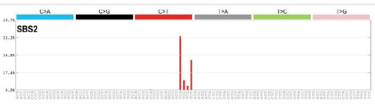
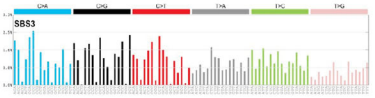
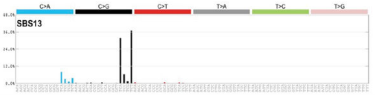
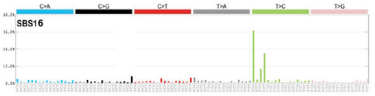
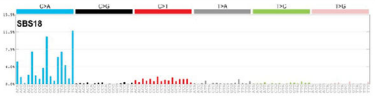
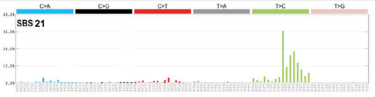
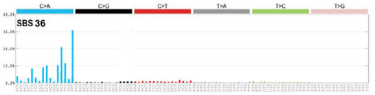
Mutation Signature	% detectible in *KRAS*^{G12C}	% detectible in *KRAS*^{other}	*p*	Proposed etiology	Mutational profile
SBS2	16%	6%	0.040	APOBEC activity	
SBS3	6%	1%	0.173	Defective DNA damage repair	
SBS4	33%	42%	0.242	Smoking signature	
SBS13	15%	11%	0.455	APOBEC activity	
SBS16	6%	17%	0.041	Unknown etiology	
SBS18	2%	10%	0.043	Reactive oxygen species	
SBS21	3%	1%	0.586	Defective DNA mismatch repair	
SBS36	8%	1%	0.089	Defective base excision repair	

Figure 3. Analysis of somatic mutational signatures in *KRAS*-mutant tumors.

Comparison of the relative frequencies of 8 detectible mutational signatures between the *KRAS*^{G12C} and other *KRAS* mutation (*KRAS*^{other}) groups, and proposed etiologies for these signatures.

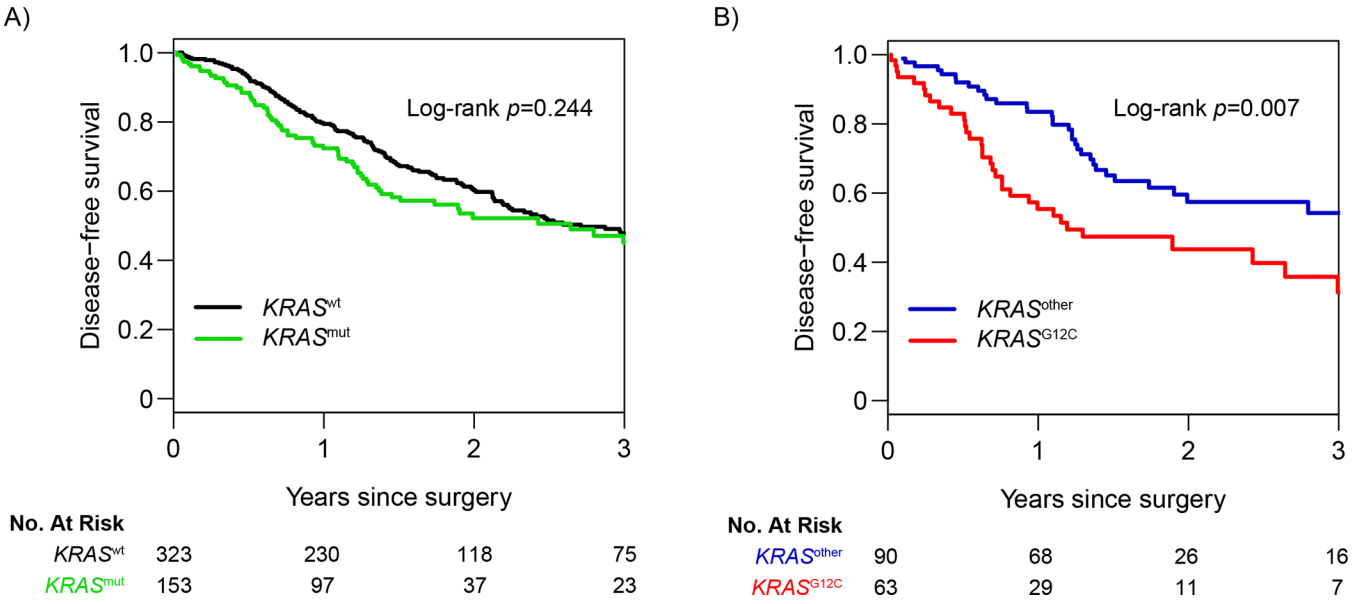


Figure 4. Association between *KRAS*-mutation status and disease-free survival in The Cancer Genome Atlas cohort (N=476).

Three-year disease-free survival for (A) all *KRAS*-mutant (*KRAS*^{mut}) tumors versus *KRAS* wild-type (*KRAS*^{wt}) tumors and for (B) *KRAS*^{G12C} tumors versus all other *KRAS*-mutant tumors (*KRAS*^{other}).

Table 1.

Comparison of clinicopathologic characteristics between the *KRAS*^{wt}, *KRAS*^{G12C}, and *KRAS*^{other} groups

Characteristic	Total Cohort (n=604)	*KRAS*^{wt} (n=374)	*KRAS*^{G12C} (n=95)	*KRAS*^{other} (n=135)
Age at resection, years	68 (62–74)	68 (62–74)	69 (64–75)	67 (61–73)
Sex				
Male	202 (33)	130 (35)	34 (36)	38 (28)
Female	402 (67)	244 (65)	61 (64)	97 (72)
Smoking status				
Never	138 (23)	125 (33)	4 (4.2)	9 (6.7)
Ever	466 (77)	249 (67)	91 (96)	126 (93)
Pack-years (n=465)	27 (15–45)	10 (0–30)	27 (16–43)	30 (14–46)
FEV1 (n=592)	94 (83–106)	95 (84–108)	90 (77–104)	94 (83–105)
DLCO (n=586)	84 (69–97)	87 (72–99)	79 (64–92)	80 (66–95)
SUVmax (n=537)	3.7 (1.9–7.2)	3.4 (1.8–6.7)	4.1 (2.3–8.1)	4.0 (2.1–7.5)
Operative approach				
VATS	521 (86)	324 (87)	79 (83)	118 (87)
Open	83 (14)	50 (13)	16 (17)	17 (13)
Operative procedure				
Lobectomy or pneumonectomy	390 (65)	245 (66)	61 (64)	84 (62)
Sublobar	214 (35)	129 (34)	34 (36)	51 (38)
Pathologic tumor size, cm	1.8 (1.2–2.8)	1.8 (1.2–2.8)	1.8 (1.3–2.7)	2.0 (1.4–3.1)
LVI (n=599)	248 (41)	150 (41)	49 (52)	49 (36)
VPI	109 (18)	70 (19)	20 (21)	19 (14)
STAS (n=544)	337 (62)	183 (55)	68 (75)	86 (70)
Histologic subtype				
Lepidic	88 (15)	59 (16)	10 (11)	19 (14)
Acinar	368 (61)	218 (58)	64 (67)	86 (64)
Papillary	43 (7.1)	28 (7.5)	4 (4.2)	11 (8.1)
Micropapillary	37 (6.1)	25 (6.7)	5 (5.3)	7 (5.2)
Solid	68 (11)	44 (12)	12 (13)	12 (8.9)
pN status (n=603)				

Characteristic	Total Cohort (n=604)	*KRAS*^{wt} (n=374)	*KRAS*^{G12C} (n=95)	*KRAS*^{other} (n=135)
N0	506 (84)	311 (83)	75 (79)	120 (89)
N1 or N2	97 (16)	62 (17)	20 (21)	15 (11)
pStage				
I	447 (74)	278 (74)	66 (69)	103 (76)
II	95 (16)	61 (16)	16 (17)	18 (13)
III	62 (10)	35 (9.4)	13 (14)	14 (10)
PD-L1 status				
None (<1%)	343 (57)	233 (62)	45 (47)	65 (48)
Low (1–49%)	85 (14)	47 (13)	15 (16)	23 (17)
High (≥50%)	176 (29)	94 (25)	35 (37)	47 (35)
Adjuvant therapy	116 (19)	68 (18)	21 (22)	27 (20)

Data are no. (%) or median (interquartile range). DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; LVI, lymphovascular invasion; PD-L1, programmed death-ligand 1; STAS, spread through air spaces; SUVmax; maximum standardized uptake value; VPI, visceral pleural invasion; wt, wild-type.

Table 2.

Multivariable analysis for disease-free survival for the total cohort and the *KRAS*^{G12C} group

Group/Variable[a]	HR[a]	95% CI	*p*
Total cohort (N=604)			
Primary tumor SUVmax	1.03	1.00–1.07	0.065
DLCO	0.99	0.98–1.00	0.031
LVI	2.36	1.43–3.91	0.001
VPI	1.66	1.10–2.51	0.015
STAS	1.81	1.02–3.23	0.044
pStage			
I	Ref	—	—
II or III	1.80	1.18–2.76	0.007
KRAS mutation status			
Non-G12C	Ref	—	—
Wild-type	1.45	0.85–2.47	0.2
G12C	1.84	1.01–3.36	0.046
KRAS^{G12C} group (n=95)			
LVI	9.57	2.20–41.54	0.003
VPI	2.25	1.03–4.94	0.042
Histologic subtype			
Lepidic, acinar, or papillary	Ref	—	—
Micropapillary or solid	2.15	0.95–4.87	0.067

CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; HR, hazard ratio; LVI, lymphovascular invasion; STAS, spread through air spaces; SUVmax, maximum standardized uptake value; VPI, visceral pleural invasion

[a]Multivariable models for all factors were adjusted for pathologic stage.