Landscape of *KRAS*^{G12C}, Associated Genomic Alterations, and Interrelation With Immuno-Oncology Biomarkers

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INTRODUCTION

KRAS is the most common driver oncogene. Promising single-agent activity from sotorasib and adagrasib in *KRAS*^{G12C}-mutant tumors has provided clinical evidence of the ability to inhibit *KRAS* signaling. However, the landscape of *KRAS*^{G12C} mutations and associated characteristics across cancer types are not well characterized.

We aimed to **1)** Investigate the prevalence of *KRAS* variants, including *KRAS*^{G12C}, **2)** Describe prevalence of co-mutations with *KRAS*^{G12C,} and **3)** Describe the relationship of *KRAS*^{G12C} with immuno-oncology (IO) biomarkers.

METHODS

We retrospectively selected and analyzed de-identified clinical records with Tempus xT tissue- and xF liquid biopsy-based NGS data from 79,004 patients with various cancer types utilizing the Tempus LENS Data & Analytics Platform. From 79,004 samples analyzed, 13,758 *KRAS*-mutated tumors were identified (**Table 1**).

Fisher's exact test was used to analyze the associations between cancer subtypes and *KRAS* variants. Logistic regression was used to study co-mutations between *KRAS*^{G12C} and other oncogenes, as well as the association between *KRAS* variants and IO biomarkers. False discovery rate-adjusted P-value (FDR-P) was used for multiple testing.

Table 1. Clinical Characteristics

	KRAS^{G12C} mutation (n=1,632)	*KRAS*$^{non\text{-}G12C}$ mutation (n=12,126)	
	n (%)	n (%)	FDR-P
Age	573	4444	**6.06E-05**
<60	157 (27.40%)	1631 (36.70%)	
≥60	416 (72.60%)	2813 (63.30%)	
Gender	1333	10713	**0.0006**
Female	748 (56.11%)	5428 (50.67%)	
Male	585 (43.89%)	5285 (49.33%)	
Self-Reported Race	802	5955	0.243545
Asian	17 (2.12%)	201 (3.38%)	
Black	107 (13.34%)	759 (12.75%)	
White	678 (84.54%)	4995 (83.88%)	
Smoking	1028	6887	**1.87E-68**
Current Smoker	257 (25.00%)	972 (14.11%)	
Ex-Smoker	616 (59.92%)	2893 (42.01%)	
Never Smoker	155 (15.08%)	3022 (43.88%)	

Table 1. Comparison of patient characteristics between *KRAS*^{G12C} and *KRAS*$^{non\text{-}G12C}$ samples across all cancer types. Of the 13,758 *KRAS*-mutated tumors, 1,632 (11.9%) tumors harbored the *KRAS*^{G12C} variant, while 12,126 harbored other *KRAS* variants (*KRAS*$^{non\text{-}G12C}$).

CONCLUSIONS

Our analysis of **real-world data** from **79,004 patients** identified significant genomic and IO biomarker differences in tumors harboring ***KRAS*^{G12C} compared to *KRAS*$^{non\text{-}G12C}$ and wildtype tumors**. . ***KRAS* variants** significantly **differed by cancer type with *KRAS*^{G12C}** accounting **for 11.9% of all *KRAS* variants.** *KRAS*^{G12C} was most prevalent in NSCLC, CRC, appendiceal cancer, TUO, pancreatic cancer and SBA, and was more often identified in females, current or prior smokers, and older patients. Oncogenic genes, *such as* ***KEAP1*, *STK11,* and *ATM*,** and key IO biomarkers, **high PD-L1 expression** and **high TMB**, were also **enriched** in ***KRAS*^{G12C} tumors**.

RESULTS

Figure 1. Prevalence of the Most Common *KRAS* Variants by Cancer Type

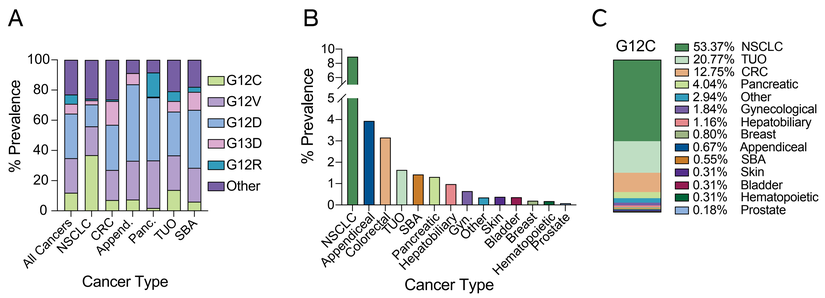

Figure 1. (A) The distribution of the top five *KRAS* variants in tumor types with the highest frequency of *KRAS*^{G12C}. (B) Frequency of *KRAS*^{G12C} mutations in 14 cancer types. (C) Percentage of all 1,632 *KRAS*^{G12C} mutated by cancer type. NSCLC, non-small cell lung cancer; CRC, colorectal cancer; Append., appendiceal; Panc., pancreatic; TUO, tumor of unknown origin; SBA, small bowel adenocarcinoma; Gyn., gynecological malignancies

Figure 2. Evaluation of Immune Biomarkers by *KRAS*^{G12C}, *KRAS*$^{non\text{-}G12C}$, and *KRAS* Wildtype Status

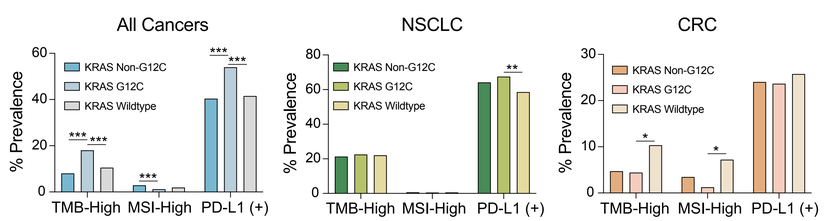

Figure 2. Comparison of TMB-high (defined as >10 mut/Mb), PD-L1-positive, and MSI-High cases between *KRAS*^{G12C} and *KRAS*$^{non\text{-}G12C}$ *and between* *KRAS*^{G12C} and *KRAS* wildtype cohorts. TMB, tumor mutational burden; MSI, microsatellite instability. *FDR-P <0.05 and was considered statistically significant; **FDR-P<0.001; ***FDR-P<0.0001.

Figure 3. Oncogenic Co-Mutations in *KRAS*^{G12C} versus *KRAS*$^{non\text{-}G12C}$ Cancers

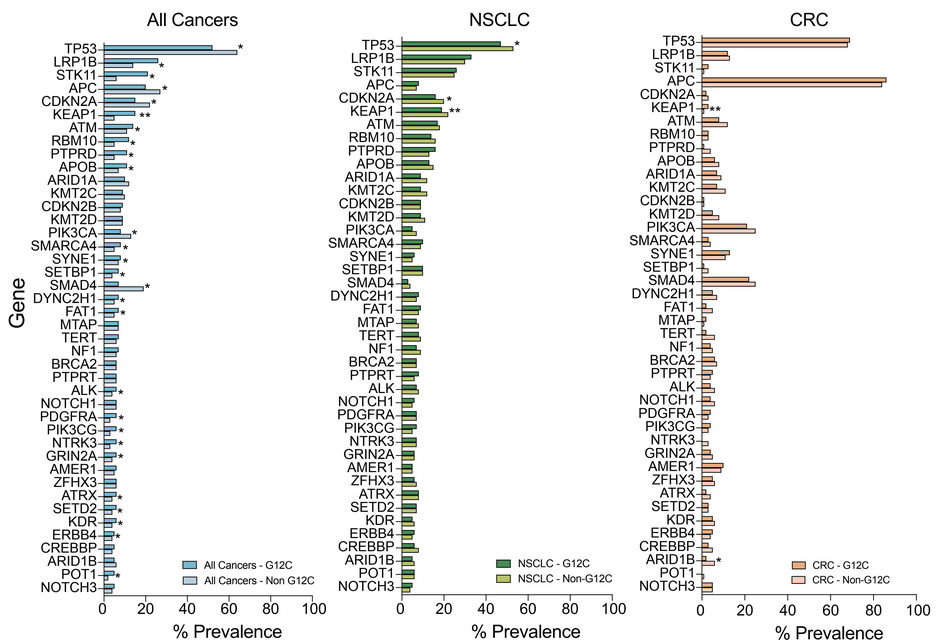

Figure 3. Comparison of co-mutations identified in the *KRAS*^{G12C} and *KRAS*$^{non\text{-}G12C}$ cohorts. Co-mutations altered in more than 5% of patients with a confirmed *KRAS* mutation were included and are shown for all cancers, NSCLC, and CRC. Logistic regression was used to calculate the odds ratio and 95% confidence intervals. *FDR-P<0.05 and was considered statistically significant. **Significant G12C status (*KRAS*^{G12C} versus *KRAS*$^{non\text{-}G12C}$) × cancer subtype (NSCLC or CRC) interaction effect on the mutation of the oncogene at FDR-P < 0.05.

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