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ORIGINAL RESEARCH

# Dissecting the Clinical Characteristics and Treatment Outcomes Correlates of *KRAS G12C*-Mutated Non-Small Cell Lung Cancer

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**Background:** *KRAS* mutation is one of the most common driver oncogenes in non-small cell lung cancer (NSCLC), and the most common mutation subtype is *G12C*. However, there is still a lack of efficacy and prognosis data related to immunotherapy, which hinders the promotion of new strategies.

**Methods:** Clinical characteristics and treatment outcomes were collected and analyzed for patients with NSCLC harboring *KRAS* mutations at West China Hospital of Sichuan University from June 2013 to March 2023.

**Results:** Among the 231 patients with *KRAS*-mutated NSCLC, 29.4% had *KRAS G12C* mutations. Compared to the *KRAS non-G12C* NSCLC group, the *KRAS G12C* NSCLC group had a greater number of pack-years. The programmed death ligand 1 expression and the proportion of patients with a high tumor mutational burden were not significantly different between the two groups. Similar patterns of *TP53, STK11*, and *CDKN2A* mutations were observed between *KRAS G12C* and *KRAS non-G12C* NSCLC groups. The median progression-free survival (PFS) (8.4 vs 7.0 months, p=0.100) and overall survival (OS) (12.1 vs 18.1 months, p=0.590) were not statistically different between *KRAS G12C* and *KRAS non-G12C*. Compared to patients with *KRAS G12C* NSCLC who did not receive immunotherapy, patients who received immunotherapy had a better objective response rate (46.2% vs 0%, p=0.002), PFS (12.2 vs 7.5 months, p=0.087) and OS (49.9 vs 11.1 months, p=0.12).

**Conclusion:** Patients with *KRAS G12C* were more likely to be smokers. Advanced *KRAS G12C* NSCLC patients who received immunotherapy had a better ORR than those who did not, suggesting that patients with *G12C* mutations are more likely to benefit from immunotherapy.

**Keywords:** non-small cell lung cancer, *KRAS G12C* mutation, *KRAS* mutation, immunotherapy, overall survival

## Introduction

Lung cancer is the leading cause of cancer-related mortality, accounting for more than 1.8 million deaths a year, and non-small cell lung cancer (NSCLC) is the most common subtype.[1–3] *KRAS* mutations are present in 25–39% of non-squamous NSCLCs.[4–6] The *KRAS G12C* mutation is present in approximately 40–46% of patients with *KRAS*-mutant NSCLC and 13–16% of those with lung adenocarcinoma[6] and is the most common *KRAS* mutation in lung cancer.[7,8]

*KRAS G12C* inhibitors represent a significant advancement in the field of targeted therapies for NSCLC.[9–18] According to the latest version of the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, the optimal first-line therapy for advanced *KRAS*-mutant NSCLC still consists of programmed cell death (ligand) 1 blockade alone or in combination with platinum-based chemotherapy,[19] and resistance to *KRAS* inhibitor monotherapy will eventually develop.[6,20,21] Given that drug combination therapy is currently a clinically recognized strategy for

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overcoming resistance to *KRAS G12C* inhibitors, combining *KRAS G12C*-targeted drugs with other drugs (such as immunotherapy and chemotherapy) may be one of the key strategies for overcoming drug resistance. The application of these compounds in clinical practice needs to be carefully considered in the context of first-line therapeutic options.

Compared with patients harboring *KRAS non-G12C* mutations, those harboring *KRAS G12C* mutations have greater tumor mutational burden (TMB) and programmed cell death ligand 1(PD-L1) expression,[22,23] and are more strongly associated with smoking history.[7,24] Based on these positive predictors of immune checkpoint inhibitors (ICIs) response, theoretically, the *G12C* subtype should have a better response to immunotherapy than the *non-G12C* subtype. Several retrospective studies addressing immunotherapy efficacy in patients with G12C mutation have yielded different results.[7,25–27] A single-center retrospective study showed that the overall response rate (ORR) (26% vs 28%, respectively, P=0.7) and progression-free survival (PFS) (3.3 vs 3.7 months, P=0.89) of patients treated with ICI-based therapy were similar in *G12C* and *non-G12C* patients, while overall survival (OS) was not described.[7] Another large retrospective study found that no significant differences in OS or PFS among patients with the main *KRAS* mutation subtypes (*G12A, G12C, G12D, G12V*, and *G13C*). Among the 25 patients treated with ICIs, patients with *KRAS G12C* mutations had a greater ORR (53.8% vs 8.3%, p = 0.030) and longer PFS (4.8 vs 2.1 months, p = 0.028) than those with *KRAS non-G12C* mutations. Consequently, a nuanced evaluation of currently available conventional treatments (eg, chemotherapy and immunotherapy) in patients with *KRAS G12C* mutations is of particular importance.

A meticulous evaluation and comparison of the baseline characteristics and outcomes of patients with *KRAS*-mutant NSCLC receiving available therapies is expected to provide a basis for the development of targeted combination therapies and improve the regimen selection and survival of patients with *KRAS G12C* mutations. Hence, we assessed the clinical characteristics and treatment outcomes of patients with *KRAS G12C*-mutated NSCLC.

# Materials and Methods

## Participants

NSCLC patients with *KRAS* mutations who were treated at West China Hospital of Sichuan University were included. Medical records were reviewed to identify patients with metastatic disease at the time of diagnosis or recurrence during the follow-up period from June 2013 to March 2023. The inclusion criteria were as follows: (1) pathologically confirmed NSCLC and (2) presence of *KRAS* mutation identified using DNA-based next-generation sequencing (NGS). The following key exclusion criteria were used: (1) the subtype of *KRAS* alterations was not reported; (2) patients aged <18 years or > 80 years; and (3) the presence of other tumors.

## Data Collection

Data on the following baseline variables were collected from medical records: age, sex, smoking history, number of pack-years of smoking, complications, Eastern Cooperative Oncology Group Performance Status, tumor proportion score of programmed cell death ligand 1, clinical stage at baseline, tumor mutational burden (TMB), tumor histology, concurrent pathogenic mutations and subtype of *KRAS* mutation at baseline. TMB were divided into three levels: low TMB(1–10 mutations/MB), medium TMB (10–19 mutations/MB), and high TMB (≥ 20 mutations/MB). Treatment-related data included therapies and treatment outcomes. The unknown baseline characteristics of patients from publications were recorded as "not available". This study was conducted following the provisions of the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 2023–649), and the requirement for individual consent for this retrospective analysis was waived. We confirmed that the data was anonymized or maintained with confidentiality.

## Efficacy and Survival Evaluation

Regarding treatment-specific outcomes in patients treated with ICIs, the best overall response (BOR) and progression status were evaluated by independent thoracic radiologists according to RECIST 1.1. PFS was defined as the time from the start of therapy to the date of disease progression or death, whichever occurred first. Patients who were alive without

disease progression were censored on the date of their last scan. Overall survival was defined as the time from the start of therapy to death. Patients who were still alive on the data lock date were censored at the date of last contact.

## Statistical Analysis

To make the clinicopathologic characteristics compatible, we adopted a propensity score matching (PSM) method in some comparisons. Descriptive statistics were used to characterize the prevalence of *KRAS G12C*, patient characteristics and treatment patterns. Categorical and continuous variables were summarized descriptively using percentages and medians. The Wilcoxon rank sum test and Kruskal–Wallis test were used to assess differences between continuous variables, and Fisher's exact test and chi-square test were used to compare associations between categorical variables. Survival curves were estimated by the Kaplan-Meier (KM) method and compared using the Log rank test. The medians with 95% confidence intervals (CIs) and numbers at risk are presented as Kaplan-Meier curves, and the Greenwood formula was used to estimate the standard errors of the estimates. Log rank tests were used to assess differences in event-time distributions.

All P values are two-sided with statistical significance defined as $p<0.05$. All the statistical analyses were performed using R (1.4.1717), SPSS statistics (version 25.0) and GraphPad Prism (version 9.0).

# Results

## Characteristics of Patients

A total of 231 patients with NSCLC harboring oncogenic *KRAS* mutations were identified, all of whom were diagnosed with NSCLC by pathologic biopsy and had *KRAS* mutations according to NGS testing (Figure 1). One hundred seventy-one of the 231 patients had locally advanced or advanced *KRAS*-mutant NSCLC, and 128 of the 171 patients were treated

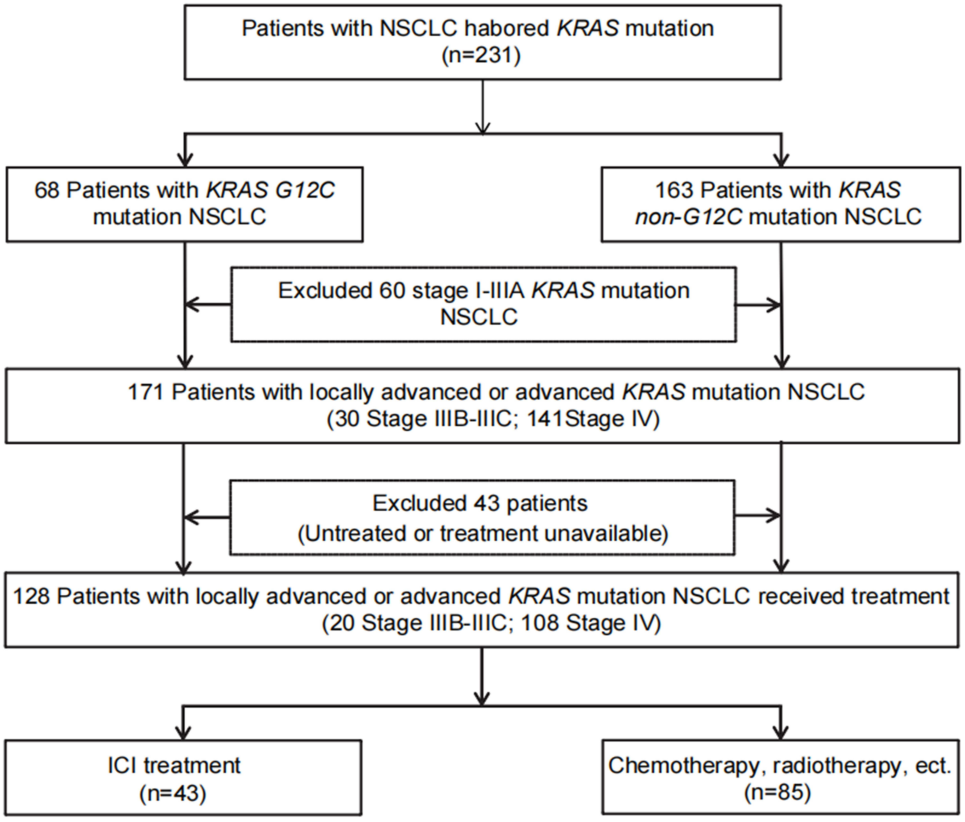


**Figure 1** All patients included in this study.

with medical therapy (Figure 1). The clinical characteristics of the 231 patients with *KRAS*-mutated NSCLC are summarized in Supplementary Table 1.

*KRAS G12C* NSCLC cases accounted for 29.4% of all *KRAS*-mutated NSCLCs (n=68/231). Other common *KRAS* driver mutations (*KRAS non-G12C*) included: *G12D* (n=44/231, 19%), *G12V* (n=39/231, 16.9%), *G12A* (n=17/231, 7.4%) and *Q61H* (n=17/231, 7.4%) (Figure 2A).

According to the comparison of the clinicopathologic features of patents with *KRAS G12C* mutations with those of patients without *KRAS G12C* mutations, patients with *KRAS G12C* mutations were significantly more likely to be smokers (83.8% vs 59.5%, p=0.001) and used tobacco more often (median 36.42 pack-years vs 21.46 pack-years, p<0.0001) (Supplementary Table 1). Comorbidities included a wide range of diseases such as COPD, hypertension, diabetes, and so on. There was a significantly higher proportion of heavy smokers in the *KRAS G12C* NSCLC group than in the *KRAS non-G12C* NSCLC group (Figure 2B). The distribution of metastatic sites in advanced NSCLC at diagnosis was similar between the *KRAS G12C* group and the *KRAS non-G12C* group (n=141, stage IV cases with known sites of metastasis) (p>0.05, Figure 2C). Additionally, the expression of PD-L1 was compared between patients with *KRAS G12C* mutations and those with *KRAS non-G12C* mutations. The median PD-L1 TPS was greater in *KRAS G12C* NSCLC patients than in *KRAS non-G12C* NSCLC patients but was not significantly different (1% vs 0.5%, p=0.600) among 169 patients who underwent PD-L1 assessment (Figure 2D).

We also compared the clinicopathologic features of patients with *KRAS G12C* and those with *KRAS G12D* mutations and confirmed that patients with *KRAS G12C* mutations were more likely to be smokers and had a greater median PD-L1 TPS, but the differences were not statistically significant (1% vs 0%, n=79, p=0.235) (Figure 2B, Supplementary Figure 1A). No difference in the ECOG PS was detected between the two groups (p=1.000) (Supplementary Figure 1B). Compared to *KRAS G12D* NSCLC, *KRAS G12C* NSCLC was more likely to metastasize to the adrenal gland (p=0.040), and no differences in other metastatic sites were identified between the two groups (p>0.05) (Supplementary Figure 1C).

## Genomic Characteristics of Patients with KRAS G12C Mutations

The genomic features of NSCLC harboring *KRAS* mutations were examined to identify whether NSCLC with *KRAS G12C* mutations differs from NSCLC with other *KRAS* mutations. All patients underwent NGS of tumor samples (n=68 *KRAS G12C*, n=163 *KRAS non-G12C*). The majority of patients had a combination of co-mutations (n=145/231, 62.8%), with *TP53* (24.68%), *STK11* (9.52%) and *CDKN2A* (8.23%) being the three most common co-mutated genes (Figure 2E). The most commonly co-mutated genes in *KRAS G12C* NSCLC included *TP53* (n=17/68, 25%), *STK11* (n=7/68, 10.2%) and *ATM* (n=7/68, 10.2%). To determine whether *KRAS G12C* has unique mutational patterns, we next compared the genomic profiles of *KRAS G12C* and *KRAS non-G12C* NSCLC. The proportion of patients with a high TMB was not significantly different between the two groups (45.4% vs 40%, n=46, p=0.627). As *TP53* and *STK11* mutations affect patient prognosis, we also compared their frequencies. The frequency of *TP53* mutation was similar in *KRAS G12C* vs *KRAS non-G12C* tumors (25% vs 24.5%, p=0.941); the results were similar for *STK11* (10.3% vs 9.2%, p=0.797) and *CDKN2A* mutation (7.4% vs 8.6%, p=0.755) (Supplementary Figure 2).

## Impact of KRAS G12C on Treatment Outcomes

We explored the clinical outcomes of 128 (55.4%) patients with locally advanced or advanced disease who received treatment. To allow integration of the clinicopathologic characteristics, we adopted a PSM method, which can minimize the discrepancies between the two groups of patients (Table 1). Patients with *KRAS G12C* NSCLC had similar objective response rate (ORR) (19.4% vs 25.6%, n=70, p=0.737), PFS (8.4 months vs 7.0 months, HR 0.619 [95% CI 0.346–1.109], n=98, p=0.100) and OS (12.1 months vs 18.1 months, HR 1.175 [95% CI 0.657–2.103], n=98, p=0.590) compared to those of patients with *KRAS non-G12C* NSCLC (Figure 3A–C).

As *KRAS G12D* was the second most common *KRAS* mutation subtype in our cohort, we also compared the clinical outcomes of patients with *KRAS G12C* with those with *KRAS G12D*, and the baseline characteristics of the patients are summarized in Supplementary Table 2. There were no differences in ORR (19.4% vs 20%, n=41, p=1.000), PFS (8.4 months vs 6.8 months, HR 0.954 [95% CI 0.326–2.793], n=63, p=0.930) or OS (12.1 months vs 27.7 months, HR 1.022 [95% CI 0.388–2.695], n=63, p=0.960) between patients with *KRAS G12C* mutation and those with *KRAS G12D* mutation (Supplementary Figure 3A–C).

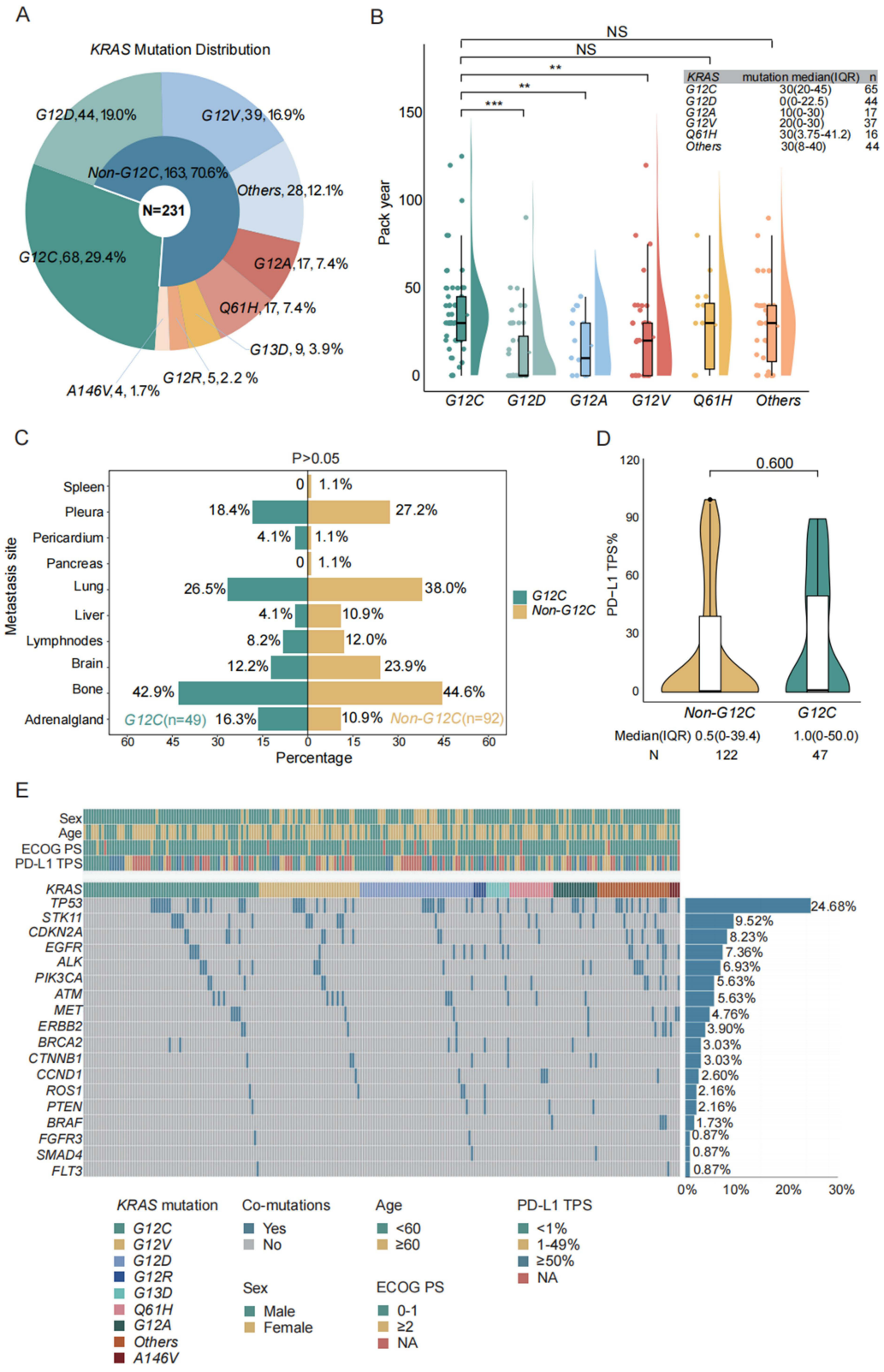


**Figure 2** (**A**) The distribution of the most common *KRAS* mutations identified in NSCLC patients at West China Hospital of Sichuan University (n=231). **(B)** The distribution of pack-years across the most common *KRAS* subtypes. **P<0.01 ***P<0.001. **(C)** Distribution of metastatic sites in stage IV *KRAS G12C* (n=49) and *KRAS non-G12C* (n=92) NSCLC patients. **(D)** PD-L1 TPS in *KRAS G12C* NSCLC (n=47) and *KRAS non-G12C* (n=122) NSCLC. **(E)** Oncoprint of the top 18 gene mutations co-occurring with *KRAS* mutation NSCLC.

**Table 1** Characteristics of Patients with Locally Advanced or Advanced KRAS NSCLC

| Clinical characteristics | Before PSM | | *p* | After PSM | | *p* |
|---|---|---|---|---|---|---|
| | ***Non-G12C*** **(n=79)** | ***G12C*** **(n=49)** | | ***Non-G12C*** **(n=49)** | ***G12C*** **(n=49)** | |
| Age, (%) | | | 0.337 | | | 0.684 |
| <60 | 29(36.7) | 23(46.9) | | 20(40.8) | 23(46.9) | |
| ≥60 | 50(63.3) | 26(53.1) | | 29(59.2) | 26(53.1) | |
| Gender, (%) | | | 0.003 | | | 1.000 |
| Male | 58(73.4) | 47(95.9) | | 47(95.9) | 47(95.9) | |
| Female | 21(26.6) | 2(4.1) | | 2(4.1) | 2(4.1) | |
| Comorbidities, (%) | | | 0.234 | | | 0.145 |
| Yes | 49(62.0) | 37(75.5) | | 30(61.2) | 37(75.5) | |
| No | 29(36.7) | 11(22.4) | | 19(38.8) | 11(22.4) | |
| NA | 1(1.3) | 1(2.1) | | 0(0.0) | 1(2.1) | |
| Smoking status, (%) | | | 0.003 | | | 0.324 |
| Current/Former | 48(60.8) | 43(87.8) | | 40(81.6) | 43(87.8) | |
| Never | 30(38.0) | 5(10.2) | | 9(18.4) | 5(10.2) | |
| NA | 1(1.3) | 1(2.0) | | 0(0.0) | 1(2.0) | |
| Pack-year (median [IQR]) | 20.00 [0.00, 36.88] | 30.00 [20.00, 45.00] | 0.001 | 30.00 [20.00, 40.00] | 30.00 [20.00, 45.00] | 0.151 |
| ECOG PS, (%) | | | 0.230 | | | 0.241 |
| 0–1 | 77(97.5) | 46(93.9) | | 49(100) | 46(93.9) | |
| ≥2 | 1(1.3) | 3(6.1) | | 0(0.0) | 3(6.1) | |
| NA | 1(1.3) | 0(0.0) | | 0(0.0) | 0(0.0) | |
| Histology, (%) | | | 0.774 | | | 0.739 |
| Adenocarcinoma | 70(88.6) | 45(91.8) | | 43(87.8) | 45(91.8) | |
| Others | 9(11.4) | 4(8.2) | | 6(12.2) | 4(8.2) | |
| Stage at diagnosis, (%) | | | 0.199 | | | 0.108 |
| III B | 9(11.4) | 6(12.2) | | 4(8.2) | 6(12.2) | |
| III C | 5(6.3) | 0(0.0) | | 4(8.2) | 0(0.0) | |
| IV | 65(82.3) | 43(87.8) | | 41(83.7) | 43(87.8) | |
| PD-L1 expression, (%) | | | 0.705 | | | 0.885 |
| <1% | 28(35.4) | 19(38.8) | | 18(36.7) | 19(38.8) | |
| 1–49% | 17(21.5) | 7(14.3) | | 10(20.4) | 7(14.3) | |
| ≥50% | 15(19.0) | 12(24.5) | | 11(22.4) | 12(24.5) | |
| NA | 19(24.1) | 11(22.4) | | 10(20.4) | 11(22.4) | |
| TMB, (%) | | | 0.257 | | | 0.054 |
| High | 7(8.9) | 5(10.2) | | 6(12.2) | 5(10.2) | |
| Low | 17(21.5) | 5(10.2) | | 14(28.6) | 5(10.2) | |
| NA | 55(69.6) | 39(79.6) | | 29(59.2) | 39(79.6) | |
| Total lines of therapy, (%) | | | 0.034 | | | 0.062 |
| 1 | 45(57.0) | 38(77.6) | | 28(57.1) | 38(77.6) | |
| 2 | 25(31.6) | 10(20.4) | | 16(32.7) | 10(20.4) | |
| ≥3 | 9(11.6) | 1(2.0) | | 5(10.2) | 1(2.0) | |

**Abbreviations**: PSM, propensity score matching; NA, not available; ECOG, eastern cooperative oncology group; PS, performance status; PD-L1, programmed cell death ligand 1; TMB, tumor mutational burden; ICI, immune checkpoint inhibitor; 1L, first line.

## Impact of KRAS G12C Mutation in Patients Receiving PD-(L)1 Blockade-Based Treatment

We compared the clinical outcomes of 43 patients with *KRAS G12C* NSCLC or *KRAS non-G12C* NSCLC who received PD-(L)1 blockade-based therapy. Due to the mismatching of clinicopathologic characteristics, we used PSM to minimize the discrepancies, and the clinicopathologic characteristics are summarized in Supplementary Table 3. When we assessed the clinical outcomes of patients receiving PD-(L)1 blockade-based therapy (including first-line and second-line therapy), we found that patients with *KRAS G12C* NSCLC had similar ORR (40% vs 42.9%, n=29, p=1.000), PFS (12.2 months vs 15.7 months, HR

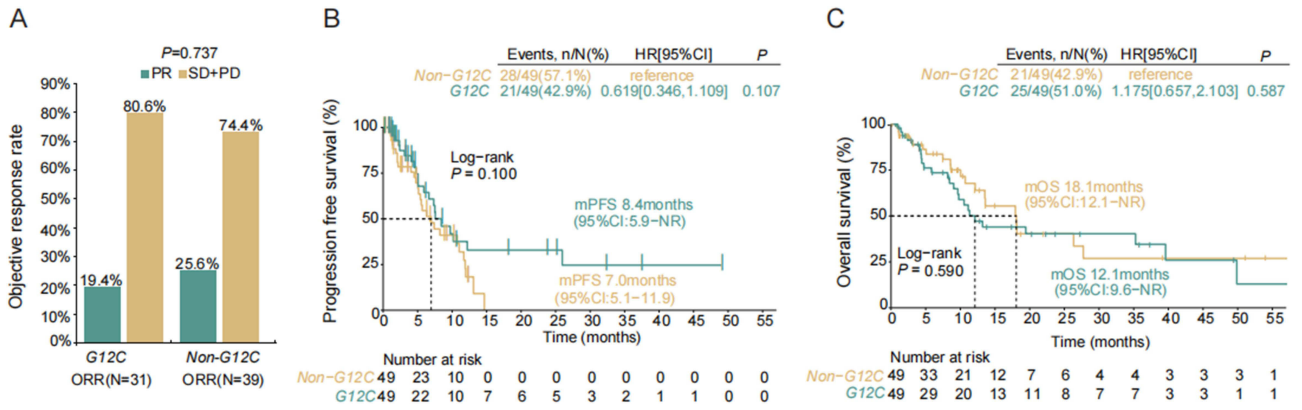


**Figure 3 (A)** Objective response rate, **(B)** progression-free survival, and **(C)** overall survival in patients with locally or advanced *KRAS G12C* NSCLC vs *KRAS non-G12C* NSCLC.

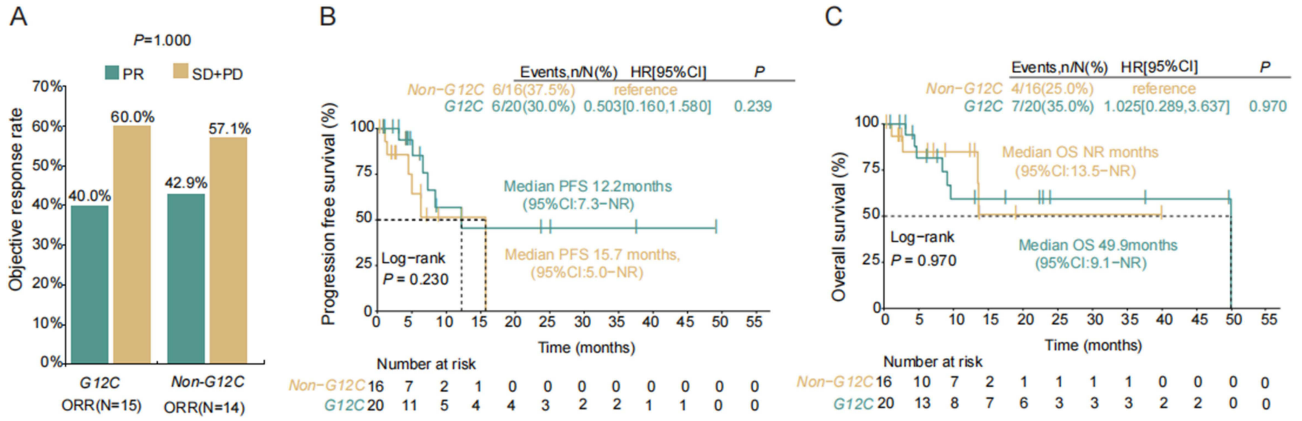


**Figure 4 (A)** Objective response rate, **(B)** progression-free survival, and **(C)** overall survival of patients with *KRAS G12C* NSCLC and *KRAS non-G12C* NSCLC who received PD-(**L**)1 blockade-based therapy (as first-line or second-line therapy).

0.503 [95% CI 0.160–1.580], n=36, p=0.230) and OS (49.9 months vs NR months, HR 1.025 [95% CI 0.289–3.637], n=36, p=0.970) compared to those of patients with *KRAS non-G12C* NSCLC (Figure 4A–C).

## PD-(L)1 Blockade-Based Therapy Outcomes in Patients with KRAS G12C NSCLC

Furthermore, we explored the clinical outcomes of 49 patients with advanced *KRAS G12C* NSCLC (first-line) who received immunotherapy. The two groups presented no significant differences in terms of patient characteristics, which are summarized in Supplementary Table 4. We found that patients with *KRAS G12C* NSCLC who received immunotherapy had a better ORR (46.2% vs 0%, n=31, p=0.002), while there were no differences in PFS (12.2 months vs 7.5 months, HR 0.447 [95% CI 0.173–1.157], n=49, p=0.087) or OS (49.9 months vs 11.1 months, HR 0.493 [95% CI 0.197–1.239], n=49, p=0.12) (Figure 5A–C).

# Discussion

Despite the emergence of targeted inhibitors, first-line treatment for patients with lung cancer harboring *KRAS G12C* mutations is still dominated by immunotherapy and chemotherapy. In-depth studies on targeted treatments for NSCLC patients with *KRAS G12C* mutations may provide reliable background information for the application of new strategies. This study enriched the clinical data on patients with lung cancer harboring *KRAS G12C* mutations and revealed that the ORR is better for patients with *KRAS G12C* who received PD-(L)1-based therapy compared to those who did not.

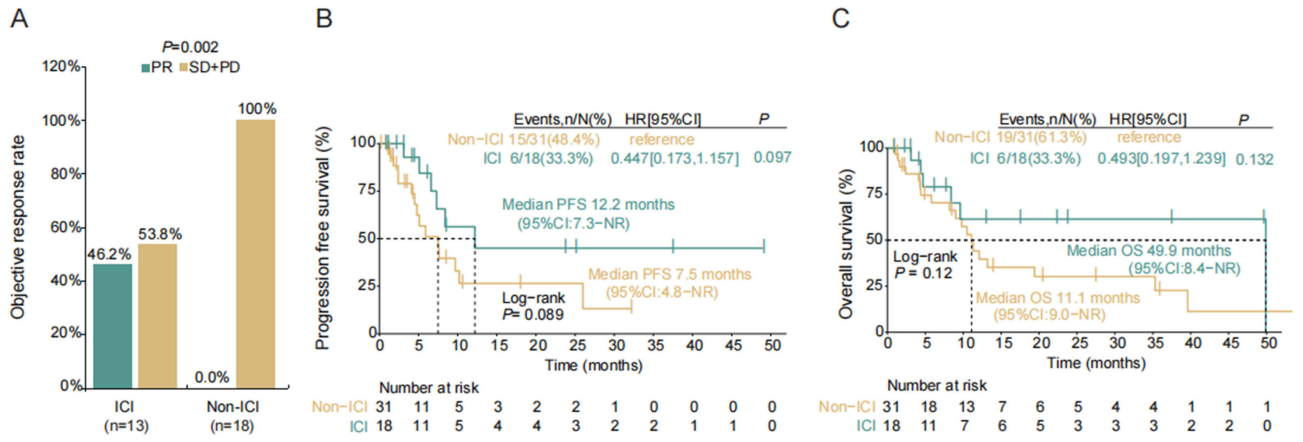


**Figure 5 (A)** Objective response rate, **(B)** progression-free survival, and **(C)** overall survival to immunotherapy (as first-line therapy) in patients with locally advanced or advanced *KRAS G12C* NSCLC.

We investigated the clinicopathologic differences among patients harboring *KRAS G12C* mutations. Notably, there were more patients with a history of smoking in the *KRAS G12C* NSCLC group than in the *KRAS non-G12C* NSCLC group, consistent with other prior reports.[7,22,28] Carcinogenic polycyclic aromatic hydrocarbons found in cigarette smoke seem to be related to the *KRAS G12C* mutation,[29] which explains why *G12C* mutation is more common in smokers.[30] In addition, we found that even among patients with other *G12* mutations (including *G12D, G12A*, and *G12V*), patients with the *G12C* mutation had the highest number of pack-years. Given that TMB and PD-L1 expression are closely related to the frequency of tobacco use in NSCLC patients, we compared the TMB and PD-L1 expression between *KRAS G12C* NSCLC and *KRAS non-G12C* NSCLC patients. In the latest NCCN guidelines, the choice of systemic regimen was adjusted from "by histology (adenocarcinoma or squamous cell carcinoma)" to "by PD-L1 status (PD-L1 ≥1% or PD-L1 <1%)". Patients with NSCLC harboring the *KRAS G12C* mutation have a greater TMB and greater PD-L1 expression. Our results are consistent with previous reports demonstrating that the *KRAS G12C* mutation is correlated with increased TMB and PD-L1 expression in lung adenocarcinoma patients.[8,22,28] Biologically, a higher TMB might leads to the production of more tumor neoantigens that are being presented to tumor antigen-specific T cells in *KRAS G12C* NSCLC than in *KRAS non-G12C* NSCLC. A previous report demonstrated that compared to the tumor microenvironment of *KRAS G12D* NSCLC, *KRAS G12C* NSCLC contains significantly more $CD8^+$ $PD1^+$ T cells and exhibits greater PD-L1 expression on both tumor and immune cells.[23]

In terms of co-mutations, *TP53, STK11* and *CDKN2A* mutations were the three most common mutations occurring with *KRAS* mutation in NSCLC,[8,22,31] which was consistent with previous studies. We also found that compared to *KRAS non-G12C* NSCLC, *KRAS G12C* NSCLC has similar co-mutation patterns of *TP53, STK11* and *CDKN2A*. We observed that the prevalence of *TP53* and *STK11* co-mutations, which were previously reported to be associated with survival and disease course,[31,32] was similar in *KRAS G12C* NSCLC and *KRAS non-G12C* NSCLC patients.

These findings suggest that among *KRAS*-mutant NSCLCs, *KRAS G12C* NSCLCs are immunologically "hotter" and may benefit more from PD-(L)1 blockade than NSCLCs with other *KRAS* subtypes. Some prior reports have suggested that there may be differences in treatment outcomes for patients with different *KRAS* mutation subtypes,[22,26,27] while other studies did not show a difference in survival.[7,25,28,33] A large cohort of Asian populations showed longer PFS in patients with KRAS G12C NSCLCs than KRAS non-G12C NSCLCs (mPFS: 3.4 vs 2.5 months, p = 0.06), while this study was conducted in patients receiving ICI monotherapy as 2nd- to 4th-line treatment.[22] A single-center retrospective study showed KRAS G12C NSCLCs (n=13) had higher ORR of ICI treatment (p = 0.030) and a significantly longer PFS (p = 0.028) than KRAS non-G12C NSCLCs (n=12);[26] Similarly, it has also been shown that KRAS G12C NSCLCs have longer PFS than KRAS non-G12C NSCLCs in patients with PD-L1>50% and receiving immunotherapy as 1L treatment.[27] However, due to the small sample size, it is not possible to analyze the differences in OS, and the reliability of the conclusions also needs to be verified. A large cohort of European populations showed KRAS G12C NSCLCs had

similar ORR (p = 0.7) and mPFS (p = 0.89) compared with KRAS non-G12C NSCLCs, however the differences in OS were not explored.[7] No significant differences in OS or PFS were observed between the major KRAS mutation subtypes (G12A, G12C, G12D, G12V, and G13C).[25] Otherwise, no difference in efficacy was observed in non-squamous NSCLC patients treated with 1L pembrolizumab immunotherapy whether they presented a KRAS G12C, non KRAS G12C or wild-type KRAS genotype.[33] The Danish queue showed that the survival in KRAS G12C NSCLCs was comparable to patients with any KRAS mutation in patients receiving anti PD-1/L1 therapies as part of routine standard of care.[28] In this study, in patients receiving conventional therapies (including ICIs, chemotherapy, radiotherapy, antiangiogenic therapy and targeted therapy), the ORR, PFS and OS were not different between patients with *KRAS G12C* mutations and those with *KRAS non-G12C* mutations. In addition, for *KRAS G12C* NSCLC patients who received ICIs, the PFS, OS and ORR were similar to those of *KRAS non-G12C* patients. This was the case even after controlling for baseline clinicopathologic characteristics, including sex, smoking status, PD-L1 TPS and TMB, which is consistent with previous reports, suggesting that *KRAS G12C* NSCLC is a distinct entity and that the outcomes cannot be solely explained by existing biomarkers. Among *KRAS G12C* NSCLC patients who received ICI-based therapy, PFS and OS were greater, but the difference was not statistically significant, which may be related to the variations in backline treatment. However, ICI treatment had a significantly better impact on the ORR in patients with *KRAS G12C* NSCLC, which was consistent with the outcomes predicted according to clinical characteristics of our cohort (including smoking history, PD-L1 TPS and TMB), suggesting that patients with *KRAS G12C* NSCLC may benefit more from immunotherapy.

The limitations of our study include its retrospective single-center design and the relatively small sample size of patients with *KRAS G12C* NSCLC. In addition, self-reported smoking history is subject to bias, and bias can be caused by unavailable data. Consequently, future large-scale multicenter or prospective studies are needed for further validation. Although any single retrospective analysis has inherent limitations, this analysis of the patient cohort revealed that immunotherapy may be a favorable option for patients with *KRAS G12C* NSCLC.

In conclusion, patients with NSCLC harboring the *KRAS G12C* mutation had greater pack-years and PD-L1 expression than patients with *KRAS non-G12C* NSCLC, with *TP53, STK11* and *ATM* being the three most common co-mutated genes. In patients with *KRAS G12C* NSCLC, compared with those who did not receive immuno-therapy as first-line therapy, patients receiving ICI-based therapy had a significantly better ORR, with a trend toward better PFS and OS, suggesting that patients with *KRAS G12C* NSCLC may benefit from receiving an immunotherapy-based regimen as first-line treatment.

## Abbreviations

NSCLC, Non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group;

ICI, Immune checkpoint inhibitor; PD-L1, Programmed cell death ligand 1; TMB, Tumor mutational burden; PSM, Propensity score matching; ORR, Overall response rate; PFS, Progression-free survival; OS, Overall survival.

## Data Sharing Statement

The data that support the findings of our study are available from the corresponding author upon reasonable request.

## Ethics Statement

This study was approved by the Ethics Committee of West China Hospital (No. 2023-649), and the data was anonymized or maintained with confidentiality. The project was performed in accordance with the Declaration of Helsinki as revised in 2013.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Yawan Jing, Yalun Li and Panwen Tian took part in drafting; all authors took part in revising or critically reviewing the article; gave final approval of the version to be published; all authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest.

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