Original Article

Efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer patients with rare *KRAS* mutations: a real-world retrospective study

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Background: Kirsten rat sarcoma homolog (*KRAS*) mutations are one of the key drivers in non-small cell lung cancer (NSCLC) and FDA-approved specific inhibitors of *KRAS*-G12C mutation are available clinically. However, inhibitors of certain KRAS mutation subtypes remain unavailable, especially rare *KRAS* mutations including G13C, G13D, and Q61H. In this study, we retrospectively investigated the outcomes of NSCLC patients with rare *KRAS*-mutation to determine if they may benefit from immune checkpoint inhibitors (ICIs).

Methods: Our retrospective study involved 240 advanced NSCLC patients with *KRAS* mutations, who visited Shanghai Chest Hospital from July 2018 to July 2021. Complete clinical and pathological data were recorded and progression-free survival (PFS) and overall survival (OS) were adopted as primary endpoints.

Results: The median follow-up time was 36.5 months (range, 30.8–42.1 months) and the median OS was 9.7 months (range, 7.6–11.8 months). Of the 240 patients evaluated, 130 (54.2%) received chemotherapy and 110 (45.8%) received ICI-based treatment. Among the patients who received chemotherapy, patients with rare *KRAS*-mutations presented worse survival outcomes (median PFS, 3.4 *vs.* 4.1 months, P=0.047; median OS, 5.2 *vs.* 7.1 months, P=0.02) than conventional *KRAS*-mutant patients. PFS and OS of rare *KRAS*-mutation patients were prolonged after immunotherapy (median PFS 7.3 *vs.* 3.4 months, P<0.001; median OS, 13.3 *vs.* 5.2 months, P<0.001) and had no significant difference compared with conventional *KRAS*-mutant patients, in part of them whose programmed death-ligand 1 (PD-L1) expression data before immunotherapy were available (n=72), patients with a higher rate of PD-L1 positive tumor cells (≥50%) presented elevated PFS and OS.

Conclusions: Despite having potential survival disadvantage compared with other NSCLC patients, rare KRAS-mutant patients (other than G12A, C, D, V) could benefit specifically from ICI-based therapy and survival outcomes are correlated with PD-L1 expression.

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Keywords: Advanced non-small cell lung cancer (advanced NSCLC); immune checkpoint inhibitor (ICI); Kirsten rat sarcoma homolog mutations (*KRAS* mutations); rare *KRAS* mutations; survival benefit

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers, which has the highest incidence and mortality rates among all malignancies worldwide (1). Among numerous oncogenic drivers, Kirsten rat sarcoma homolog (*KRAS*) mutations are commonly observed in NSCLC patients (2,3) and its prognostic impact remains unclear. Since its discovery in 1982, *KRAS* has been considered as an undruggable driver protein for decades. However, recent studies suggest that sotorasib and adagrasib could specifically target G12C mutation, which were approved by Food and Drug Administration (FDA) in 2021 (4,5). Nevertheless, other *KRAS* inhibitors are undergoing trials, which indicate that NSCLC patients with non-G12C mutation require other options.

Immune checkpoint inhibitors (ICIs) have gained extraordinary outcomes among a subset of NSCLC patients in recent years and have become one of the standard treatments for advanced NSCLC. A study reported that patients with *KRAS* mutation can benefit from immunotherapy (6). However, these studies either included all *KRAS*-mutant patients or emphasized on patients with G12A, G12C, G12D and G12V mutations (7-9), which are dominant *KRAS* mutations accounting for around 80% of *KRAS*-mutant NSCLC patient population. Meanwhile, few studies specifically investigated rare *KRAS* mutations including G13C, G13D, Q61H, G12S and other rare mutations on exon 12, 13 and 61, hence the therapeutic effect of ICIs on these patients needs to be explored.

In this study, we presented data on the characteristics and treatment outcomes of real-world advanced *KRAS*-mutant NSCLC patients, and investigated the potential value of immunotherapy on advanced NSCLC patients with rare *KRAS* mutations. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-372/rc).

Highlight box

Key findings

- Rare Kirsten rat sarcoma homolog (*KRAS*) mutations (including G13C, G13D, Q61H, G12S) led to poor prognosis for advanced non-small cell lung cancer (NSCLC) patients, however these patients can benefit from immunotherapy.

What is known and what is new?

- For NSCLC patients carrying *KRAS* mutations, immune checkpoint inhibitors (ICIs) provide longer survival than chemotherapy. Certain inhibitors are available specifically for patients with G12C mutation.
- Rare *KRAS* mutations may lead to poor prognosis. For advanced NSCLC patients carrying rare *KRAS* mutations, immunotherapy offers improved survival benefit compared to patients with conventional *KRAS* mutations.

What is the implication, and what should change now?

- Our study suggests that for advanced NSCLC patients with certain rare *KRAS* mutations, ICI-based treatment may provide more favorable survival than classical chemotherapy, which was not previously reported in literature due to the rarity of this population.

Methods

Data and patients

Over 500 patients with *KRAS* mutations were identified from patients who received treatment at Shanghai Chest Hospital from July 2018 to July 2021. Stage IIIC and IV NSCLC patients were enrolled, and certain patients were excluded: (I) patients who were positive for other driver mutations; (II) patients who missed follow-up or with incomplete clinical information; (III) patients with tumor of other organs; (IV) early staged patients. Two hundred and forty patients met the criteria, and clinical information such as gender, age, smoking history, histology, co-mutant genes was obtained from the database. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shanghai Chest Hospital Ethics Committee (No. IS21117) and informed consent was taken from all the patients.

Molecular detection

Patients' tissue samples were obtained for pathological diagnosis, next generation sequencing (NGS) and programmed death-ligand 1 (PD-L1) detection before therapeutic treatment. NGS (LungCureCDx, Burning Rock, Suzhou, China) was used to detect mutations, and PD-L1 expression was detected via the immunohistochemistry (IHC) 22C3 pharmDx assay (Agilent Technologies China, Beijing, China).

Therapeutic schedule

One hundred and ten (45.8%) patients were treated with ICIs, of which, 35 received ICI monotherapy and 75 received combined therapy with chemotherapy or anti-angiogenic therapy. Sixty-four patients received first-line immunotherapy and 40 of them received second-line immunotherapy, while the remaining 130 patients received chemotherapy regimens such as pemetrexed/paclitaxel/docetaxel plus carboplatin/cisplatin, or bevacizumab/anlotinib. Some patients received radiotherapy if appropriate.

Endpoints and follow-up

Primary endpoints were progression-free survival (PFS) and overall survival (OS). PFS is defined as the time from initiation of first-line therapy to disease progression or death, and OS is defined as the time from initiation of first-line therapy to death or last follow-up. For patients receiving immunotherapy, initiation was defined as the first day they received immunotherapy. Relevant data were obtained from the patients' clinical records combined with verification through telephone interview. Disease progression was assessed by senior radiologists in accordance to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), with periodic radiology tests including high resolution chest computed tomography (HRCT) scan and abdominal ultrasound scan performed every 6–8 weeks, brain magnetic resonance imaging (MRI) performed every 6 months.

Statistical analysis

All statistical analyses were performed using SPSS (ver. 27.0 IBM Corporation, Armonk, NY, USA). Chi-squared and Fisher's exact test were used to compare categorical variables between two groups. Survival analyses of median PFS, median OS, and between-group differences were determined via the Kaplan-Meier method and log-rank test. Cox proportional hazards model was further used to perform univariate and multivariate analyses of independent survival risk factors. P values were two-sided and differences were considered statistically significant when $P<0.05$.

Results

Patient characteristics

Two hundred and forty patients were enrolled (*Figure 1A*). The cohort included 211 males and 29 females, and the majority (n=234, 97.5%) had clinical stage IV disease at the time of diagnosis. One hundred and forty-nine (62.0%) of patients had a smoking history. The median age was 66 years (range, 32–86 years) and the median follow-up time was 36.5 months (range, 30.8–42.1 months) by December 15th, 2022. Tumor progression occurred in 211 patients and 180 of patients passed away. One hundred and forty (58.3%) patients had distant metastasis, 101 (42.1%) had bone metastasis and 41 (17.1%) had brain metastasis. Genetic sequencing revealed the distribution of *KRAS* mutational subtypes, including G12A (n=25, 10.4%), G12C (n=68, 28.3%), G12D (n=50, 20.8%), G12V (n=36, 15.0%) and rare mutations (n=61, 25.4%) (*Figure 1B*,*1C*). All variables were balanced between patients with conventional mutations (G12A, G12C, G12D and G12V) and rare mutations and results did not differ statistically ($P>0.05$). Other baseline characteristics of all patients are shown in *Table 1*.

Survival analysis

Survival analysis was conducted to reveal whether survival differences exist among *KRAS* subtypes. Of the 240 advanced NSCLC patients with *KRAS* mutations, 36 patients with G12V and 68 patients with G12C had more PFS (G12C P=0.39, G12V P=0.08) and OS (G12C P=0.88, G12V P=0.29) benefit after standard therapy, however neither was statistically significant. As for the 25 G12A patients, 50 G12D patients and 61 rare mutation patients, potential differences in survival outcomes were not observed (*Figure 2A*,*2B*, Figure S1A,S1B).

Moreover, we analyzed patients who received standard treatments exclusive of immunotherapy (n=130) and patients who received ICIs (n=110). In patients who received standard treatments, patients harboring rare *KRAS*

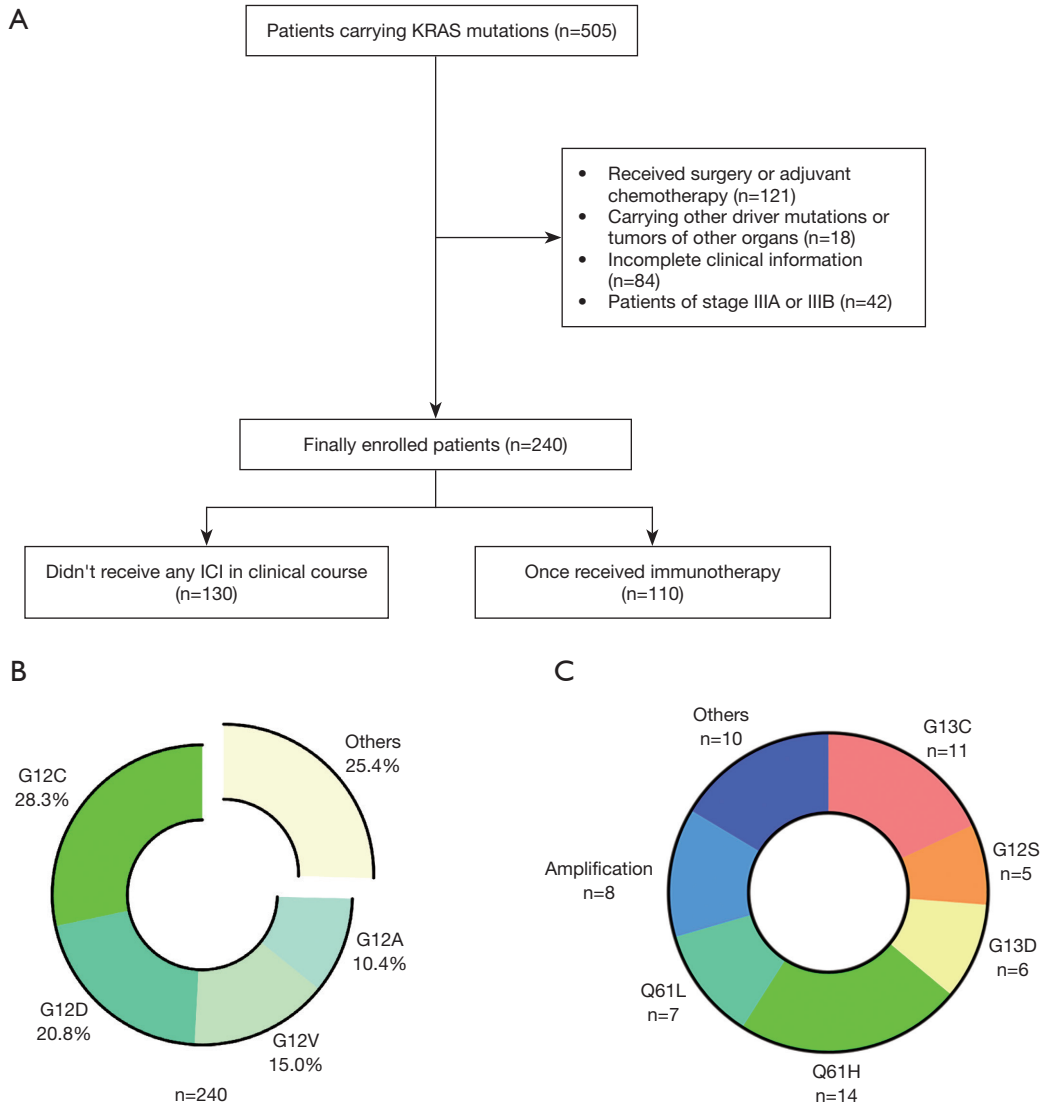

Figure 1 The enrolling process (A), distribution of KRAS mutation subtypes (B), and specific composition of rare *KRAS* mutations (C), the others included G12L (n=1), G12F (n=3), A146T (n=1), A59G (n=1), Q61K (n=1), G13Y (n=1), A59T (n=1) and G12I (n=1). KRAS, Kirsten rat sarcoma homolog; ICI, immune checkpoint inhibitor.

mutations (including G13C, G13D, Q61H, etc.) have shorter PFS (3.4 *vs.* 4.1 months, P=0.047) and OS (5.2 *vs.* 7.1 months, P=0.02) (*Figure 2C,2D*) than other subtypes. As for patients who received immunotherapy, differences in survival outcomes were not observed among different *KRAS* subtypes (Figure S1C,S1D).

The 110 patients who received ICIs therapy had significantly longer PFS and OS (median PFS 7.6 *vs.* 3.8 months, P<0.001; median OS, 18.5 *vs.* 6.1 months, P<0.001, *Figure 3A,3B*), compared with the 130 patients who received other standard therapies. Comparisons were further conducted in subgroups and significant differences were observed among patients who did or did not receive ICIs in the G12D group (median PFS 13.4 *vs.* 3.8 months, P=0.002; median OS, 30.1 *vs.* 8.6 months, P=0.002, Figure S2A,S2B) and rare mutation patients (median PFS 7.3 *vs.* 3.4 months, P<0.001; median OS, 13.3 *vs.* 5.2 months, P<0.001, *Figure 3C,3D*). Similarly, a trend towards longer OS appeared in G12C and G12V patients (Figure S2C,S2D).

Cox proportional-hazards models were used to analyze

Table 1 Baseline characters of all patients

Characteristics	G12A, G12C, G12D & G12V patients (n=179), n (%)	Rare mutation patients (n=61), n (%)	P value
Gender			0.28
Male	155 (86.9)	56 (91.8)	
Female	24 (13.1)	5 (8.2)	
Age (years)			0.71
<65	89 (49.7)	32 (52.5)	
≥65	90 (50.3)	29 (47.5)	
Smoking history			0.97
Never-smoker	68 (38.0)	23 (37.7)	
Former/current smoker	111 (62.0)	38 (62.3)	
TNM stage			0.65
IIIC	4 (2.2)	2 (3.3)	
IV	175 (97.8)	59 (96.7)	
Histology			0.09
Adenocarcinoma	163 (91.1)	50 (82.0)	
Squamous	6 (3.4)	6 (9.8)	
Others	10 (5.6)	5 (8.2)	
Brain metastasis			0.34
Yes	33 (18.4)	8 (13.1)	
No	146 (81.6)	53 (86.9)	
Extrathoracic metastasis			0.44
Yes	107 (59.8)	33 (54.1)	
No	72 (40.2)	28 (45.9)	
Bone metastasis			0.16
Yes	80 (44.7)	21 (34.4)	
No	99 (55.3)	40 (65.6)	
Treatment			0.75
Chemotherapy	97 (54.2)	33 (54.1)	
First-line ICI	46 (25.7)	18 (29.5)	
Second or back line ICI	36 (20.1)	10 (16.4)	
Radiotherapy			0.10
Yes	40 (22.3)	20 (32.8)	
No	139 (77.7)	41 (67.2)	

TNM, tumor, lymph node and metastasis; ICI, immune checkpoint inhibitor.

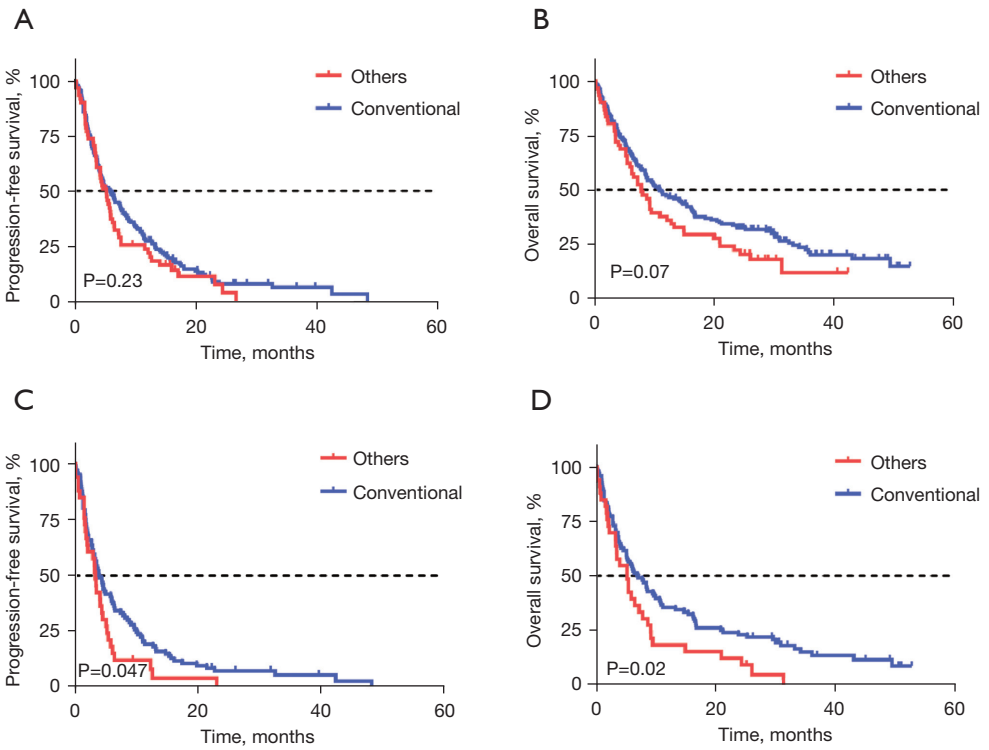

Figure 2 Comparison of progression-free survival (A) and overall survival (B) between all conventional mutation patients (G12ACDV) and other rare mutation patients; and comparison of progression-free survival (C) and overall survival (D) between conventional mutation patients and other rare mutation patients who were treated with chemotherapy.

other factors that may influence PFS and OS. P<0.1 was considered significant to increase sensitivity. After univariate and multivariate analyses, we found that TNM stage (P=0.04), histology (P=0.03), immunotherapy (P<0.001), G12C (P=0.04) and other rare *KRAS* subtypes (P=0.04) were significant factors affecting PFS (*Table 2*), and receiving immunotherapy was the independent risk factor for OS (P<0.001, P<0.001, *Table 3*).

PD-L1 expression and concurrent mutations

Among patients who received immunotherapy, PD-L1 expression was observed in 72 patients. Compared to PD-L1 negative tumors, patients with PD-L1 positive tumors, especially those with higher rate of PD-L1 positive tumor cells (≥50%), had elevated PFS and OS (*Figure 4A-4D*).

STK11 and *KEAP1* have been considered a negative prognosis factor for *KRAS* patients (10,11). Regrettably, due to insufficiency of the NGS test kit, only *STK11* mutational conditions of patients were detected. Fifty-two (21.6%) patients had positive *STK11* mutations and they had significant less survival benefit than other patients, regardless of whether they accepted immunotherapy or not (*Figure 5A-5D*). On the other hand, the most common co-mutation, TP53 (n=131, 54.5%) had minimal effect over patients' OS (P=0.93).

Discussion

KRAS mutations are highly prevalent in solid tumors like lung, colorectal and pancreatic cancers, found in about 30% of lung cancer patients and less in Asian patients (12), and may cause worse prognosis in advanced and metastatic NSCLC (13). *KRAS* mutations are involved in many vital oncogenic processes like proliferation, differentiation and survival through different intracellular downstream pathways such as rapidly accelerated fibrosarcoma (*RAF*)-mitogen-activated protein kinase (*MEK*)-extracellular signal-regulated kinase (*ERK*) pathway and phosphatidylinositol 3-kinase (*PI3K*)-*AKT* pathway (14). However, owing to its intrinsic characteristics such as its picomolar affinity for GDP and GTP, *KRAS* was considered

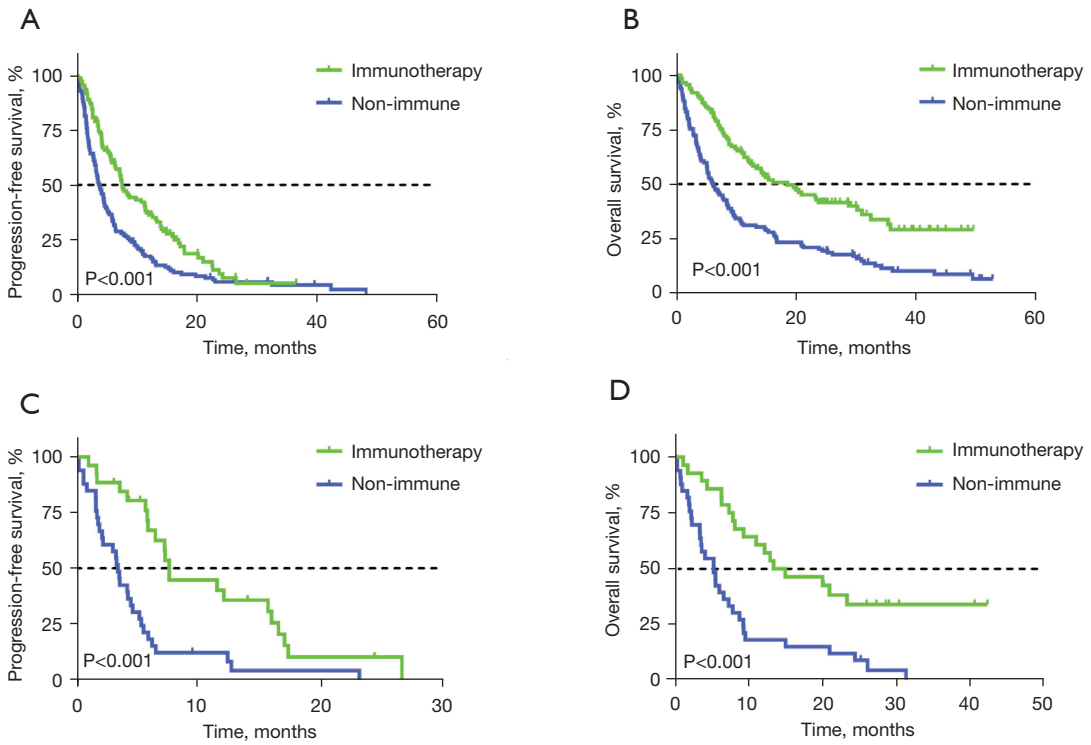

Figure 3 Comparison of progression-free survival (A) and overall survival (B) between all immunotherapy and non-immune patients; and comparison of progression-free survival (C) and overall survival (D) between rare mutation patients who received ICIs or not. ICI, immune checkpoint inhibitor.

as an "undruggable" target (15), which resulted in the delayed discovery of targeted inhibitors two decades later than *EGFR*. Nevertheless, after the approval of sotorasib in 2021, which targets the G12C subtype, standard first-line treatment for *KRAS* mutation patients continues to follow the principles of driver-gene-negative NSCLC treatment, which is based on cytotoxic chemotherapy or immunotherapy. In addition, a meta-analysis suggested that immunotherapy brought *KRAS*-mutant patients greater OS benefit than wild type (WT) patients (16), indicating that with the introduction of immunotherapy, the efficacy of immunotherapy on *KRAS*-mutant patients is still worth exploring.

Since the discovery of new targetable allosteric regulatory sites on G12C in 2013 (15), which suggested that *KRAS* signaling process could be interfered through irreversible binding of covalent inhibitors seemed to be the most effective way to overcome *KRAS*, and correlative research gained increasing attention. As the most common *KRAS* pathogenic variant, *KRAS* G12C occurs in around 30% of all cases (2,17). With the discovery of enhanced G12C inhibitors, research about *KRAS* mutation lung cancers mainly emphasized on the G12C subtype, while others focused on major subtypes like G12A, G12D and G12V. With the approval of sotorasib and adagrasib by the FDA and research conducted on other G12C, G12D, or pan-*KRAS* inhibitors (18,19), rare subtype inhibitors are being evaluated with novel compounds including RMC-6236.

Usually classified as 'others', the remaining portion of rare *KRAS* mutations manifests in 10% to 20% (and potentially higher in smokers) of the *KRAS* mutation lung cancer patient population (20,21). These rare mutations include more than 10 subtypes and are located on codon 12, 13 and 61 of the *KRAS* gene, which indicate that they do not share a common molecular structure which as a result, researchers may deem developing specific targeting inhibitors to be uneconomical and less important. Furthermore, rare *KRAS* mutations were often reported as impact factor for inferior survival, despite slight difference in grouping from our study's definition, like codon 12 *vs.* codon 13 according to Yu *et al.* (22). In this situation,

Table 2 Univariable and multivariable analysis for PFS

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Gender			0.77			
Male	Reference					
Female	0.941	0.628–1.412				
Age (years)			0.66			
<65	Reference					
≥65	0.941	0.716–1.235				
Smoking history			0.92			
No	Reference					
Yes	0.985	0.745–1.303				
TNM stage			0.06*			0.04*
III	Reference			Reference		
IV	0.469	0.207–1.063		0.392	0.160–0.962	
Histology			0.01*			0.03*
Adenocarcinoma	Reference			Reference		
Squamous	1.096	0.579–2.074	0.78	0.973	0.479–1.978	0.94
Others	1.827*	1.057–3.159*	0.03*	2.179*	1.232–3.852*	0.007*
KRAS mutation type			0.36			0.21
G12V	Reference			Reference		
G12A	1.279	0.734–2.228	0.39	1.210	0.691–2.121	0.51
G12C	1.495*	0.952–2.350*	0.08*	1.624*	1.030–2.559*	0.04*
G12D	1.303	0.808–2.100	0.28	1.387	0.859–2.239	0.18
Others	1.564*	0.989–2.474*	0.06*	1.631*	1.016–2.617*	0.04*
Primary brain metastasis			0.12			
No	Reference					
Yes	1.330	0.931–1.901				
Primary extrathoracic metastasis			0.62			
No	Reference					
Yes	1.071	0.815–1.409				
Primary bone metastasis			0.96			
No	Reference					
Yes	1.007	0.764–1.326				
Immunotherapy			<0.001*			<0.001*
No	Reference			Reference		
Yes	0.593	0.449–0.782		0.518*	0.387–0.692*	<0.001*
Radiotherapy			0.87			
No	Reference					
Yes	1.026	0.749–1.404				
Targeted therapy			0.19			
No	Reference					
Yes	0.833	0.635–1.092				

*, significant P values. PFS, progression-free survival; KRAS, Kirsten rat sarcoma homolog; TNM, tumor, lymph node and metastasis; HR, hazard ratio; CI, confidence interval.

Table 3 Univariable and multivariable analysis for OS

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Gender			0.77			
Male	Reference					
Female	0.934	0.592–1.473				
Age (years)			0.47			
<65	Reference					
≥65	0.471	0.831–1.492				
Smoking history			0.66			
No	Reference					
Yes	0.935	0.692–1.264				
TNM stage			0.44			
III	Reference					
IV	0.725	0.321–1.637				
Histology			0.22			
Adenocarcinoma	Reference					
Squamous	1.215	0.640–2.306	0.55			
Others	1.606	0.910–2.675	0.10			
KRAS mutation type			0.41			0.16
G12V	Reference			Reference		
G12A	1.225	0.678–2.213	0.50	1.255	0.694–2.270	0.45
G12C	1.196	0.739–1.935	0.47	1.369	0.844–2.221	0.20
G12D	1.088	0.651–1.820	0.75	1.137	0.680–1.903	0.62
Others	1.530*	0.944–2.480*	0.09*	1.757*	1.080–2.858*	0.02*
Primary brain metastasis			0.40			
No	Reference					
Yes	1.175	0.805–1.715				
Primary extrathoracic metastasis			0.57			
No	Reference					
Yes	1.090	0.811–1.465				
Primary bone metastasis			0.92			
No	Reference					
Yes	1.015	0.753–1.367				
Immunotherapy			<0.001*			<0.001*
No	Reference			Reference		
Yes	0.462	0.341–0.628		0.441	0.324–0.600	
Radiotherapy			0.31			
No	Reference					
Yes	1.196	0.849–1.686				
Targeted therapy			0.24			
No	Reference					
Yes	0.838	0.625–1.123				

*, significant P values. OS, overall survival; KRAS, Kirsten rat sarcoma homolog; TNM, tumor, lymph node and metastasis; HR, hazard ratio; CI, confidence interval.

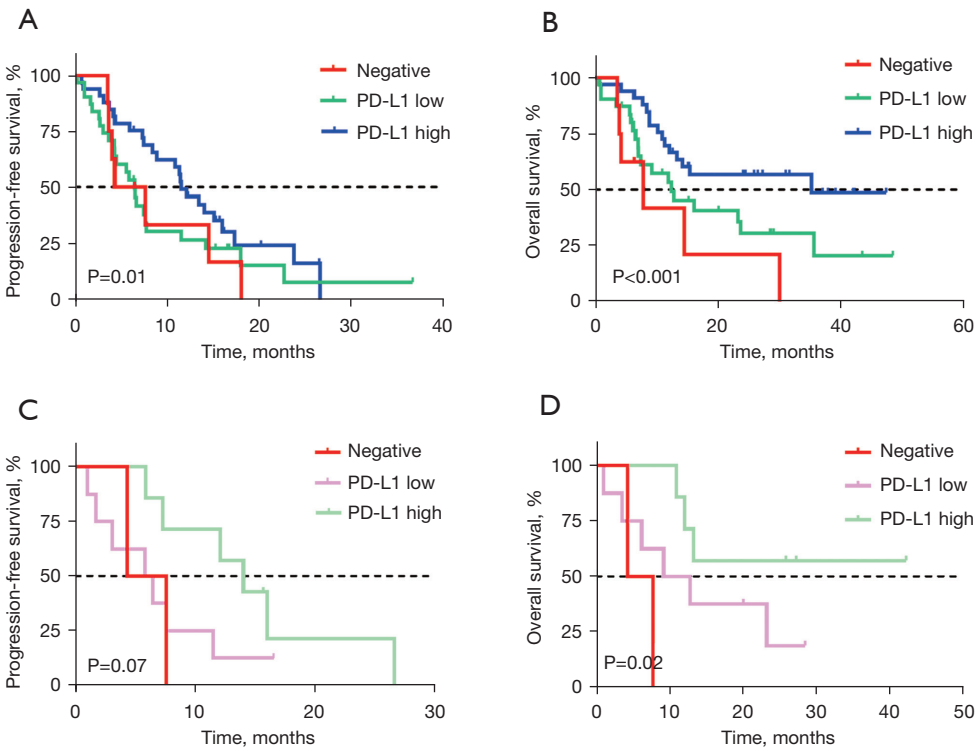

Figure 4 For all immunotherapy patients (PD-L1 expressions were available in 72 of them), their PFS (A) and OS (B) elevated with their expression of PD-L1 rate (P=0.01, P<0.001). For rare mutation patients receiving ICIs (17 with available PD-L1 expressions), their PFS (C) and OS (D) also elevated with their expression of PD-L1 rate (P=0.07, P=0.02). PD-L1, programmed death-ligand 1; PFS, progression-free survival; OS, overall survival; ICI, immune checkpoint inhibitor.

the efficacy of ICIs in patients with *KRAS*-mutated lung cancer may provide another option for targeted inhibitors. A study suggested that immunotherapy confers significant survival benefits over chemotherapy in all *KRAS* mutational status (16). Our research found that rare *KRAS* mutation patients had worse PFS and OS than major *KRAS*-subtypes when their therapeutic schedules were exclusive of ICIs, with a median PFS of 3.4 months and median OS of 5.2 months. However, the same result was not observed in the whole population inclusive of immunotherapy patients. Hence, we analyzed the difference in survival outcome between patients receiving ICIs or not, and found that the effect of ICIs on rare *KRAS* mutation patients were the most statistically significant (P<0.001). This suggests that advanced NSCLC patients with rare *KRAS* mutation with poor prognosis can benefit more from immunotherapy. As we mentioned above, in previous studies these rare *KRAS* mutation patients were to a certain degree neglected, this study may provide reference for future clinical practice.

We also investigated the survival benefit of immunotherapy treatment lines on patients, however significant difference between first-line and second-line treatment were not observed (Figure S3A,S3B). On the other hand, high PD-L1 expression could elevate the efficacy of ICIs on rare *KRAS*-mutant patients. This indicates that PD-L1 expression may have greater impact than other factors on these patients.

STK11/KRAS co-mutations are associated with poor prognoses and may predict primary resistance to ICI (10). We found that 21.6% (n=52) patients are *KRAS/STK11* co-mutated in our study. The co-mutations predict worse OS and PFS than *KRAS*-mutated *STK11* WT. While receiving immunotherapy could bring better outcomes than standard chemotherapy, the difference in survival outcomes between *STK11* mutation type (MT) and WT still exists. While analyzing survival outcomes of immunotherapy, we found that ICI had a statistically significant effect on G12D patients, and these patients may see greater improvement than rare mutation patients. Our results, however, contradict some other studies (9,23), and this may be due to

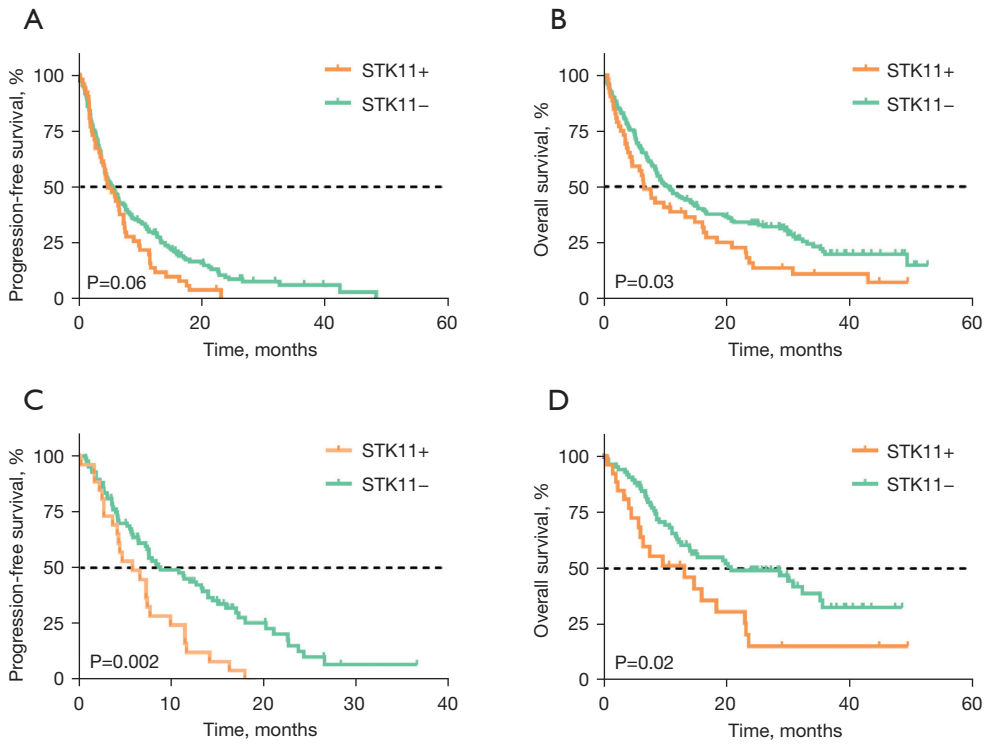

Figure 5 *STK11/KRAS* co-mutation have brought patients worse PFS (4.7 *vs.* 5.5 months, P=0.06, A) and OS (6.6 *vs.* 10.6 months, P=0.03, B), such differences were also observed in patients received immunotherapy (PFS: 5.8 *vs.* 8.8 months, P=0.002, C; OS: 13.3 *vs.* 20.9 months, P=0.02, D). KRAS, Kirsten rat sarcoma homolog; PFS, progression-free survival; OS, overall survival.

selection bias present in our study. Literature has suggested that ICIs combined with chemotherapy seems to achieve longer OS than immunotherapy alone for *KRAS*-mutant advanced NSCLCs (16). We found no difference between the two regimens (Figure S3C,S3D). Notably, up to 87.9% (n=211) of our patients were male, though *KRAS* mutations were more frequently found in male and east-Asians (21,24).

There are several limitations in our study. First, it is a retrospective single-center study with a sample size of 240, which selection bias may exist, like our population was consisted mainly of patients from Shanghai and surrounding areas, as well as the higher proportion of male patients. Second, due to practical reasons, information gathered was incomplete, such as the lack of PD-L1 expression status of partial patients and KEAP1 mutation situations of all patients.

Conclusions

In conclusion, our study suggests that among *KRAS* mutations, rare mutations (other than G12A, C, D, V) presented worse survival outcomes in advanced NSCLC patients. Though specific inhibitors are unavailable, ICI-based treatment could provide significant survival improvement than chemotherapy, which correlates with patients' PD-L1 expression.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-372/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shanghai Chest Hospital Ethics Committee (No. IS21117) and informed consent was taken from all the patients.

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