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Original Article

KRAS mutation subtypes in metastatic non-small cell lung cancer

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Abstract: The aim of this study is to determine the clinicopathologic features of KRAS mutant metastatic non-small cell lung cancer (NSCLC) patients and to determine the clinical, prognostic and survival differences between subtypes and their relationship with response to treatment. A total of 101 patients with KRAS mutant metastatic non-small cell lung cancer treated in 3 oncology centers between 2013 and 2024 were included in this retrospective, multicenter study conducted in Turkey. Molecular analysis was confirmed by next generation sequencing (NGS; QIAGEN Clinical Insight Interpretation, United States). The Kaplan-Meier method was used to compare progression-free (PFS) and overall survival (OS) times between KRAS subgroups. KRAS G12C mutation was detected in 69 (68.3%) and KRAS non-G12C mutation in 32 (31.7%) patients. In both groups, the majority of patients were male (91.3% vs. 84.4%), smokers or former smokers (92.8% vs. 90.6%) and histologically had adenocarcinoma subtype (88.4% vs. 81.3%). There was no statistically significant difference in PD-L1 expression (21.7% vs. 34.4%, P: 0.132). In the KRAS non-G12C group, the most common mutations were G12V 15 (14.8%) and G12D 6 (5.9%). The most common co-mutation accompanying KRAS G12C mutation was TP53 (23%), while the most common co-mutation accompanying KRAS non-G12C was Rictor (36.3%). While 23 (33.3%) patients with KRAS G12C mutation developed brain metastasis, this rate was 14 (43.8%) in the KRAS non-G12C mutation group (P=0.312). Median follow-up was 15.30 (0.3-112.0) months. The objective response rate (ORR) with first-line treatment was 47.5% in the KRAS G12C group and 48.3% in the KRAS non-G12C group (P: 0.657). Median PFS was 4.46 (2.85-6.08) months in the KRAS G12C group and 5.23 (3.46-6.99) months in the KRAS non-G12C group (P: 0.852). Median overall survival was 14.46 (8.34-20.58) months in the KRAS G12C group and 15.36 (5.01-25.71) months in the KRAS non-G12C group (P: 0.201). In KRAS mutant metastatic NSCLC patients, no significant difference was found between KRAS subtypes (G12C vs. non-G12C) in terms of clinical, prognostic and survival data.

Keywords: Non-small cell lung cancer, KRAS G12C, KRAS non-G12C, survival outcomes

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Recently, dramatic improvement in survival times was achieved with molecular investigation and targeted therapies in patients with driver mutations. In patients without driver mutations, immune checkpoint inhibitors used in combination with monotherapy or chemotherapy have resulted in a significant reduction in mortality in advanced stage patients [1, 2]. However, in second and subsequent steps, response rates to both chemotherapy and immunotherapies are between 6% and 20% and progression-free survival is around 2-4 months [3, 4]. Targeted therapies are widely used in patients with EGFR' mutation, ALK, ROS1 and RET rearrangement. However, although the Kirsten rat sarcoma viral oncogene

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homolog (KRAS) mutation is found in 20-40% of lung adenocarcinomas (26% in the Western population, 11% in Asians, 30% in smokers, 10% in non-smokers), no targetable agent was found for many years [5].

Activating mutations in KRAS are among the most commonly detected oncogenic driver mutations in solid cancers. These are most commonly found in lung, pancreatic and colon cancers. The NRAS mutation is more common in melanoma and HRAS mutation in bladder cancer. The most common subtypes are G12C, G12V and G12D at codons 12 and 13. The most common co-mutations are TP53 (40%), STK11/LB1 (32%) and CDKN2A (19.8%) [6].

Sotorasib is a small molecule that specifically and irreversibly inhibits KRAS G12C. In a phase 2 study, in which the majority of patients (81%) had previously progressed with platinum-based chemotherapy and immunotherapy, the activity of sotorasib was evaluated and an objective response (3.2% complete response, 33.9% partial response) was obtained in 37.1% of patients. Median progression-free survival was 6.8 months and median overall survival was 12.5 months [7]. In addition to the availability of targetable agents for KRAS G12C, KRAS mutation is also known to be important in terms of disease prognosis. It has been associated with high postoperative disease recurrence and poor survival in patients with NSCLC (especially adenocarcinoma) [8, 9]. Furthermore, subtypes of KRAS mutations were shown to provide different prognostic and predictive benefits [10]. Although KRAS mutation was evaluated as a prognostic and/or predictive factor in meta-analyses, heterogeneity in patient characteristics and lack of treatment diversity limit the interpretation of these studies.

Although various predictive markers (PDL-1, CPS, TMB, MSI) were identified for patients who may benefit from immunotherapies, there is no optimal marker. In addition to studies showing more significant results with immunotherapies in patients with KRAS mutations, there are also studies showing similar efficacy to those without KRAS mutations. In a retrospective study of 282 patients with advanced NSCLC treated with immunotherapy, the efficacy was compared between patients with KRAS mutations and patients without KRAS mutations. Similar objective response rate (ORR: 18.7% vs. 14.4%, P=0.348), progression-free survival (PFS: 3.09 vs. 2.66 months, P=0.584) and overall survival (OS: 14.29 vs. 11.14 months; P=0.682) were found. However, a trend towards improved objective response rates and prolonged progression-free survival was shown in patients with KRAS mutations and programmed death ligand 1 (PD-L1) ≥50%, which was not observed in the non-KRAS mutant cohort [11]. Therefore, more research is needed about the role of immunotherapy for KRAS patients and the correlation with PD-L1 expression.

In patients with KRAS G12C-mutant NSCLC, the lifetime incidence of brain metastases is approximately 40% [12] and some studies found no significant difference in the development of brain metastases in KRAS mutant and non-mutant patients.

In this study, we aimed to determine the clinicopathologic features of KRAS mutant metastatic NSCLC patients, the differences between subtypes in terms of clinical, prognostic and survival data, and their relationship with response to treatment (chemotherapy and immunotherapy) to contribute to the literature about this topic.

Material and methods

A total of 101 patients treated for KRAS mutant metastatic NSCLC between January 2013 and June 2024 at 3 oncology centers in Turkey were included in this retrospective, multicenter study based on clinical record reviews. The inclusion criteria were as follows: histologically diagnosed NSCLC, confirmed by next generation sequencing (NGS; QIAGEN Clinical Insight Interpretation, United States), and KRAS mutation and presence of radiologically demonstrated metastases (Stage 4).

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp, Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables, mean ± SD and median (min-max) for continuous variables. The Mann Whitney U test was used for pairwise group comparisons. Pearson chi square test and Fisher's exact test were used to compare categorical variables.

Table 1. Comparison of sociodemographic and clinical variables according to KRAS mutation

Variable	Total N=101	KRAS mutation		P
		Non-G12C N=32 (31.7%)	G12C N=69 (68.3%)	
Age				
Mean ± SD	64.30±9.41	64.12±10.23	64.37±9.08	0.886[c]
Median (min-max)	64.0 (40-87)	63.0 (43-86)	65.0 (40-87)	
≤65	54 (53.5)	18 (56.3)	36 (52.2)	0.702[a]
>65	47 (46.5)	14 (43.8)	33 (47.8)	
Sex, n (%)				
Male	90 (89.1)	27 (84.4)	63 (91.3)	0.318[b]
Female	11 (10.9)	5 (15.6)	6 (8.7)	
Smoking status, n (%)				
Never	8 (7.9)	3 (9.4)	5 (7.2)	0.706[b]
Current or former	93 (92.1)	29 (90.6)	64 (92.8)	
Histologic features, n (%)				
Adenocarcinoma	87 (86.1)	26 (81.3)	61 (88.4)	0.120[b]
Squamous	7 (6.9)	2 (6.3)	5 (7.2)	
Adenosquamous	2 (2.0)	0 (0)	2 (2.9)	
NOS	5 (5.0)	4 (12.5)	1 (1.4)	
Stage at diagnosis, n (%)				
Stage 2	8 (7.9)	2 (6.3)	6 (8.7)	0.055[b]
Stage 3	13 (12.9)	8 (25)	5 (7.2)	
Stage 4	80 (79.2)	22 (68.8)	58 (84.1)	
Local lung recurrence, n (%)				
No	97 (96.0)	32 (100)	65 (94.2)	0.304[b]
Yes	4 (4.0)	0 (0)	4 (5.8)	
Liver Metastasis, n (%)				
No	82 (81.2)	29 (90.6)	53 (76.8)	0.098[a]
Yes	19 (18.8)	3 (9.4)	16 (23.2)	
Lung metastasis, n (%)				
No	54 (53.5)	17 (53.1)	37 (53.6)	0.963[a]
Yes	47 (46.5)	15 (46.9)	32 (46.4)	
Brain metastasis, n (%)				
No	64 (63.4)	18 (56.3)	46 (66.7)	0.312[a]
Yes	37 (36.6)	14 (43.8)	23 (33.3)	
Bone metastasis, n (%)				
No	53 (52.5)	21 (65.6)	32 (46.4)	0.072[a]
Yes	48 (47.5)	11 (34.4)	37 (53.6)	
Adrenal metastasis, n (%)				
No	77 (76.2)	23 (71.9)	54 (78.3)	0.483[a]
Yes	24 (23.8)	9 (28.1)	15 (21.7)	
Other metastasis, n (%)				
No	69 (68.3)	19 (59.4)	50 (72.5)	0.188[a]
Yes	32 (31.7)	13 (40.6)	19 (27.5)	
PD-L1 status, n (%)				
Unknown	55 (54.5)	15 (46.9)	40 (58)	0.132[a]
<1%	20 (19.8)	6 (18.8)	14 (20.3)	
1-49%	16 (15.8)	9 (28.1)	7 (10.1)	
>50%	10 (9.9)	2 (6.3)	8 (11.6)	

Best response to first-line treatment, n (%)				
SD	2 (2.3)	0 (0)	2 (3.4)	0.657[b]
PR	37 (42.0)	12 (41.4)	25 (42.4)	
CR	5 (5.7)	2 (6.9)	3 (5.1)	
PD	44 (50.0)	15 (51.7)	29 (49.2)	
Number of treatment				
Not received	13 (12.9)	3 (9.4)	10 (14.5)	0.463[b]
1	39 (38.6)	13 (40.6)	26 (37.7)	
2	27 (26.7)	8 (25.0)	19 (27.5)	
3	14 (13.9)	3 (9.4)	11 (15.9)	
4	5 (5.0)	3 (9.4)	2 (2.9)	
6	2 (2.0)	1 (3.1)	1 (1.4)	
8	1 (1.0)	1 (3.1)	0 (0.0)	
Mortality				
Alive	18 (17.8)	8 (25)	10 (14.5)	0.199[a]
Ex	83 (82.2)	24 (75)	59 (85.5)	
Follow-up (month)				
Mean ± SD	21.98±21.20	24.34±19.62	20.89±21.94	0.449[c]
Median (min-max)	15.30 (0.3-112.0)	15.76 (0.6-78.1)	14.46 (0.3-112.0)	

a: Pearson Chi Square test, b: Fisher's Exact test, c: Mann Whitney U test, P<0.05 was considered statistically significant.

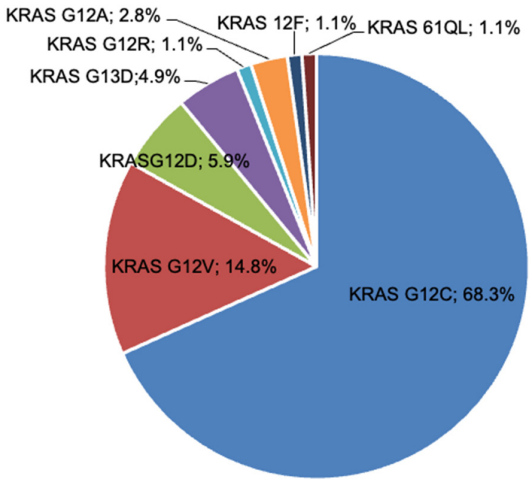

Figure 1. Frequency of KRAS mutations in patients with Non Small-Cell Lung Cancer (NSCLC).

The Kaplan Meier method was used to compare progression-free and overall survival times between KRAS subgroups. P<0.05 was considered statistically significant.

Institutional review board statement: Ethical approval was granted by the Institutional Review Board of Adnan Menderes University Hospital (Aydın, Turkey) with reference number E-53043469-050.04-658220, approved on 20 December 2024.

Results

KRAS G12C mutation was detected in 69 (68.3%) and KRAS non-G12C mutation in 32 (31.7%) patients. In both groups, the majority of patients were male (91.3% vs. 84.4%), smokers or former smokers (92.8% vs. 90.6%) and histologically had adenocarcinoma subtype (88.4% vs. 81.3%).

There was no statistically significant difference between the two groups in terms of metastatic sites. In the KRAS G12C group, 23.2% of patients had liver metastases, 46.4% had lung metastases, 33.3% had brain metastases, 53.6 had bone metastases, and 21.7% had adrenal metastases. In the KRAS-non G12C group, 9.4% of patients had liver metastases, 46.4% had lung metastases, 43.8% had brain metastases, 34.4% had bone metastases, and 28.1% had adrenal metastases.

There was no statistically significant difference in PD-L1 expression (21.7% vs. 34.4%, P: 0.132) (**Table 1**). In the KRAS non-G12C group, G12V 15 (14.8%) and G12D 6 (5.9%) mutations were most common (**Figure 1**). The most common co-mutation accompanying KRAS G12C mutation was TP53 (23%), while the most common co-mutation accompanying KRAS non-G12C was Rictor (36.3%) (**Figure 2**). Me-

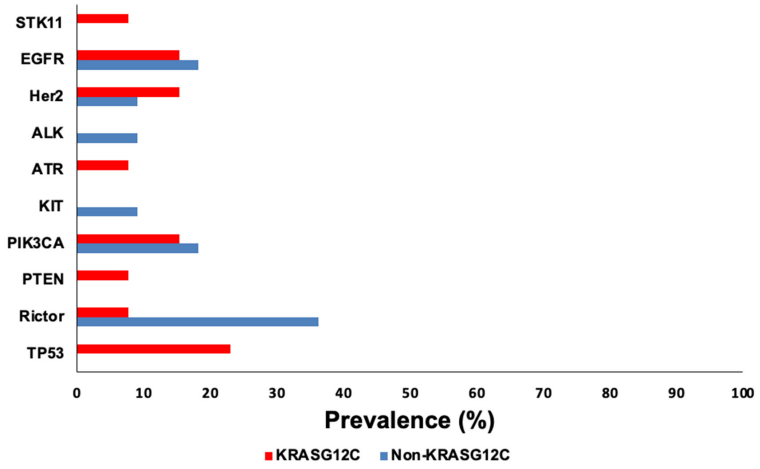

Figure 2. Comparison of oncogenic comutations for KRAS G12C and KRAS non-G12C cohorts.

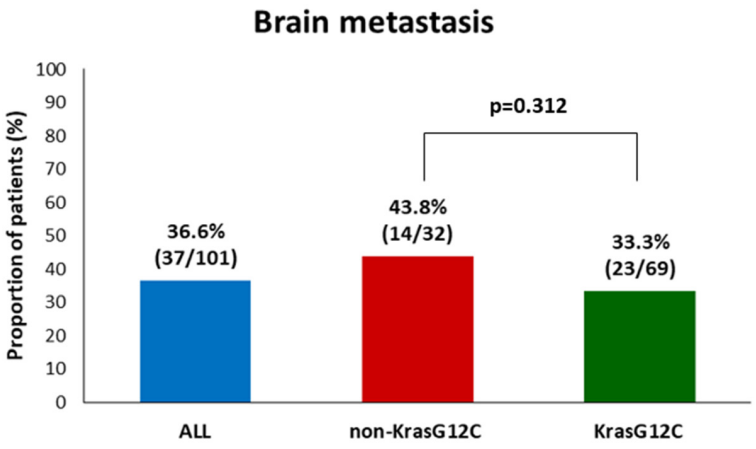

Figure 3. The frequency of brain metastasis.

Table 2. First-line therapy regimens in all patients

Değişkenler	N	%
First-line therapy		
Not received	12	12.0
Platinum + gemcitabine	9	9.0
Platinum + gemetrexed	30	30.0
Platinum + taxane	37	37.0
Platinum + etoposide	3	3.0
Single agent chemo	4	4.0
Single agent pembrolizumab	2	2.0
Pembrolizumab + Chemo	1	1.0
Alectinib	1	1.0
Erlotinib	1	1.0

dian follow-up was 14.4 months in the KRAS G12C mutant group and 15.7 months in the KRAS non-G12C mutant group. Brain metastasis developed in 23 (33.3%) of KRAS G12C mutation patients compared to 14 (43.8%) in the KRAS non-G12C mutation group (P=0.312) (**Figure 3**). While the majority of patients received first-line cytotoxic chemotherapy, two patients with PD-L1 expression >50% received single agent pembrolizumab, and one patient received pembrolizumab plus chemotherapy, One EGFR mutation patient received erlotinib and one ALK mutation patient received alectinib (**Table 2**). As seen in **Table 1**, sociodemographic and clinical variables did not have statistically significant differences between KRAS mutation groups (P> 0.05).

Median follow-up was 15.30 (0.3-112.0) months. The objective response rate (ORR) with first-line treatment was 47.5% in the KRAS G12C group and 48.3% in the KRAS non-G12C group (P: 0.657) (**Figure 4**). Median PFS was 4.46 (2.85-6.08) months in the KRAS G12C group and 5.23 (3.46-6.99) months in the KRAS non-G12C group (P: 0.852) (**Table 3**; **Figure 5**). Median overall survival was 14.46 (8.34-20.58) months in the KRAS G12C group and 15.36 (5.01-25.71) months in KRAS non-G12C group (P: 0.201) (**Table 4**; **Figure 6**).

Discussion

KRAS mutations vary according to tumor histology, smoking history and ethnicity. KRAS mutations are found in 30% of lung adenocarcinomas and 5% of squamous cell carcinomas. It affects Caucasians more [13]. Studies found a strong association between tobacco and cigarette smoking and KRAS mutation, as in TP53

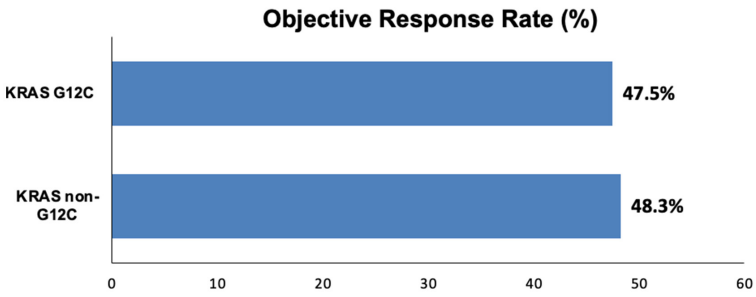

Figure 4. Objective response rates with first-line treatment.

Table 3. Comparision of progression free survival rates

Variable	2-year %	5-year %	Median (95% CI)	p
Overall	4.8	3.6	4.53 (3.20-5.86)	
Age				
≤65	2.2	2.2	4.53 (3.43-5.62)	0.192
>65	7.7	5.1	5.70 (3.29-8.10)	
Sex				
Male	5.3	3.9	5.23 (3.91-6.54)	0.830
Female	-	-	3.23 (2.12-4.34)	
KRAS mutation subtype				
Non-G12C	3.8	-	5.23 (3.46-6.99)	0.852
G12C	5.2	3.4	4.46 (2.85-6.08)	
Brain metastasis				
No	5.6	3.7	4.53 (2.71-6.35)	0.799
Yes	3.3	-	4.53 (2.96-6.09)	

Kaplan Meier curve, Long rank test, P<0.05 was considered statistically significant.

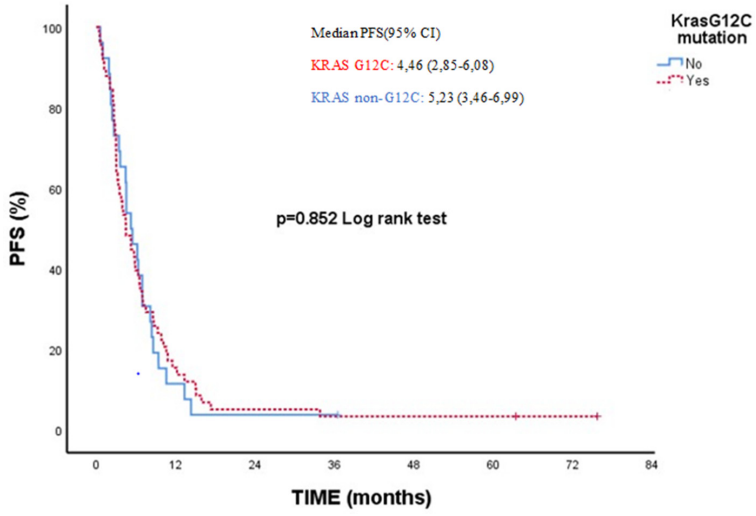

Figure 5. Progression free survival of KRAS G12C and KRAS non-G12C cohorts.

mutation [14, 15]. At least nine types of mutations were identified according to the base or amino acid substitution (G12C 39%, G12V 21.8%, G12D 15.6%, G12A 9.3%, G12S 1.5%, G13D 6.2%, G13C 3.1%, G12R 1.5% and G12F 1.5%). According to the Sanger Registry (http://www.sanger.ac.uk), the G12C mutation is most common in lung cancer, while the G12D mutation is most common in colon cancer.

In our study, the majority of patients had adenocarcinoma histology and were smokers. Since we included only KRAS mutation patients, similar to previous studies, the most common mutations were G12C (68.3%), G12V (14.8%) and G12D (5.9%), respectively.

KRAS/TP53 rearrangements exhibit high PD-L1 expression and this is important in terms of identifying patients who may benefit clinically from pembrolizumab treatment [16]. In our study, high PD-L1 expression was also found in patients with KRAS/TP53 rearrangements. However, survival data could not be analyzed due to the small number of patients who received immunotherapy.

In a study including various cancer types with KRAS mutation, no significant difference was found between KRAS G12C and non-KRAS G12C in NSCLC in terms of high PD-L1 expression similar to our study (P: 0.38) [17].

Researchers reported that KRAS subtypes show different sensitivity patterns to therapeutic agents. For example, they reported that G12C mutation is associated with decreased response to cisplatin

Table 4. Comparision of overall survival rates

Variable	2-year %	5-year %	Median (95% CI)	P
Overall	36.4	12.6	15.36 (11.14-19.59)	
Age				
≤65	38.5	19.7	14.56 (6.16-22.96)	0.328
>65	34.0	6.4	15.36 (9.41-21.32)	
Sex				
Male	33.3	10.6	14.26 (9.58-18.94)	0.074
Female	62.3	27.7	38.00 (5.29-70.70)	
KRAS mutation subtype				
Non-G12C	37.5	14.8	15.36 (5.01-25.71)	0.201
G12C	35.8	10.9	14.46 (8.34-20.58)	
Brain metastasis				
No	34.4	13.1	14.40 (9.63-19.16)	0.397
Evet	39.7	11.1	19.16 (10.70-27.62)	

Kaplan Meier, Log rank test, P<0.05 was considered statistically significant.

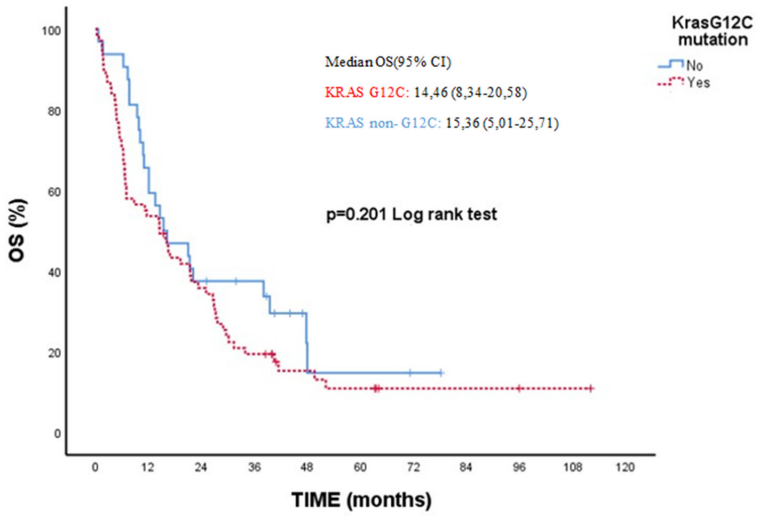

Figure 6. Overall survival of KRAS G12C and KRAS non-G12C cohorts.

but increased sensitivity to paclitaxel and pemetrexed, G12D mutation is associated with decreased response to paclitaxel and increased sensitivity to sorafenib, while G12V mutation has a stronger cisplatin sensitivity and a moderate pemetrexed resistance compared to wild-type [15].

In our study, such an analysis could not be performed due to the insufficient number of patients. However, there was no statistically significant difference in objective response rates between KRAS G12C and non-KRAS G12C groups to first-line treatment with platinum-based chemotherapy (47.5% vs. 48.3%, P: 0.657).

In a study evaluating the incidence of brain metastasis in KRAS G12C mutant NSCLC, the incidence of brain metastasis was 35.1% in the entire KRAS mutant patient population, 37.2% in KRAS G12C and 33.5% in KRAS non-G12C, and no significant difference was found between KRAS subtypes (P: 0.26) [18]. Similarly, in our study, the incidence of brain metastasis in the entire patient population was 36.6% and no significant difference was found between KRAS subtypes in terms of brain metastasis incidence (P: 0.312). Again, when the entire patient population is considered, no statistically significant differences were found in PFS (P: 0.799) and OS (P: 0.397) between patients with and without brain metastases.

In a study conducted in the Netherlands to determine the prognostic significance of KRAS G12C mutation in stage 4 NSCLC, patients were treated with first-line (chemo) immunotherapy and overall survival was compared. Median OS was 15.5 months in KRAS G12C and 14.0 months in KRAS non-G12C (P: 0.67) and it was reported that KRAS subtype did not affect OS [19]. Confirming this study, no significant difference was found between KRAS subtypes in terms of PFS and OS with first-line treatment in our study.

A targetable genomic alteration is not identified in almost half of lung adenocarcinomas. Recent studies identified amplification of RICTOR, an mTORC2-specific cofactor, as a novel target in NSCLC [20]. According to the Cancer Genome Atlas (TCGA) database, RICTOR amplification was found in 10.3% of adenocarcinomas and 15.8% of squamous cell carcinomas of the lung (see TCGA Data Portal) [21, 22].

RICTOR amplification is associated with improved sensitivity to mTOR1/2 inhibitors.

In our study, we found RICTOR mutation accompanying KRAS mutation in a total of 5 patients and all of them had adenocarcinoma histology. In the KRAS non-G12C group, RICTOR mutation accounted for 36.3% of the patients with co-mutation. In this group, where there is currently no proven targeted treatment option, mTOR inhibitors may be a new therapeutic option.

The important limitations of our study are that it was retrospective and included a small number of patients. The lack of patients using current treatment options (sotorasib, adagrasib) among patients with KRAS G12C mutation may have affected the survival data. In addition, due to the insufficient number of patients receiving immunotherapy, we could not identify a patient group that will benefit from immunotherapy-based therapeutic regimens. Therefore, we believe that prospective studies with large cohorts including current treatment options are needed.

Conclusions

No significant differences were found between KRAS subtypes (G12C vs. non-G12C) in KRAS mutant metastatic NSCLC patients in terms of clinical, prognostic and survival data.

Disclosure of conflict of interest

None.

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