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ORIGINAL RESEARCH ARTICLE

Impact of KRAS Mutations on Clinical Outcomes of Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer Receiving Anti-PD-1/PD-L1 Therapy

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Abstract

Background KRAS is the most frequently mutated gene in non-small cell lung cancer (NSCLC), however conflicting data are available on its role as a biomarker.

Objective The aim of our work was to investigate the impact of KRAS mutations on response and survival outcomes in advanced non-squamous NSCLC patients treated with immune checkpoint inhibitors alone or in combination with chemotherapy.

Patients and Methods We retrospectively identified 119 patients, most of whom (58%) were KRAS wild type. For each patient we evaluated overall survival (OS), progression-free survival (PFS), and disease control rate (DCR). An exploratory analysis was performed among KRAS mutated patients to investigate the impact of specific KRAS mutations on response and survival outcomes.

Results After a median follow-up of 10.3 months, the median OS was 14.9 months (95% confidence interval [CI] 7.6–22.7) in wild-type KRAS patients versus 14.7 months (95% CI 8.0–19.5) in mutated KRAS patients ($p=0.529$). No differences were detected between the two groups in terms of PFS and DCR. Patients with a KRAS G12C mutation reported survival and response outcomes that were not statistically different from those of patients with other KRAS mutations.

Conclusion Our data confirmed that KRAS mutational status is not associated with survival and response outcomes in advanced non-squamous NSCLC patients treated with immunotherapy alone or combined with chemotherapy.

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Key Points

In this retrospective analysis, survival and response outcomes of patients with KRAS-mutant non-small cell lung cancer (NSCLC) were not statistically different from those of patients with wild-type KRAS NSCLC receiving immune checkpoint inhibitors alone or combined with chemotherapy for advanced disease.

Among mutated KRAS patients, no differences were found according to the subtype of mutation (G12C vs. others).

KRAS mutational status was shown to be neither a prognostic nor predictive biomarker in patients with advanced non-squamous NSCLC treated with immunotherapy or chemoimmunotherapy.

1 Introduction

The prognosis of patients with non-small cell lung cancer (NSCLC) has significantly improved in recent years thanks to advances in molecular diagnostics and targeted treatments. A comprehensive genomic screening may identify aberrations in oncogenes, including EGFR, ALK, ROS1, BRAF, and MET, and specific inhibitors for all these targets are now available [1]. Mutations of Kirsten rat sarcoma viral oncogene homolog (KRAS) are the most frequent genomic alteration in NSCLC, accounting for approximately 30% of non-squamous NSCLCs [1]. KRAS encodes an intracellalur protein belonging to the family of guanosine triphosphate (GTP)-binding proteins, and it is responsible for the control of cellular signaling transduction and the regulation of cell proliferation. After GTP binds to mutated KRAS protein, its constitutive activation triggers downstream effectors, including EGFR, RAF, MEK, PI3K and AKT, leading to uncontrolled tumour cell proliferation and survival [1–3]. KRAS mutations are missense and result in amino acid changes in codons 12, 13 or 61. The most common amino acid change is from a glycine to a cysteine in codon 12 (G12C) that is detected in 13% of lung cancers; others are G12A, G12D, G12R, G12V, G13D, Q61L, and Q61H [4, 5]. KRAS G12C and G12V are more common in smokers, while G12D is the most prevalent KRAS codon alteration in former or non-smokers [6].

While several agents were developed to target most of the gene mutations in NSCLC patients, until recently, no targeted therapy was available for mutated KRAS patients. Chemotherapy and immunotherapy represent two options for this subgroup of patients, who are often smokers and with higher PD-L1 expression levels [7, 8]. Moreover, genomic analyses showed that KRAS-mutant tumours are heterogeneous because of concomitant mutations such as TP53, CDKN2A/2B, STK11, and KEAP1, which give the tumour different biological properties and therapeutic vulnerability [1, 6, 9, 10]. For example, concomitant KRAS and TP53 mutations, found in about 40% of KRAS-mutant patients, are associated with increased tumour cell proliferation and inflammation, and higher expression levels of PD-L1, resulting in higher response rates to immunotherapy [6, 11]. These factors may contribute to the sensitivity of mutated KRAS tumours to immune checkpoint inhibitors (ICIs). In the multicentric retrospective IMMUNOTARGET study, ICIs were more effective in mutated KRAS patients than in other subgroups of oncogene-addicted tumours. In 271 KRAS-mutant patients, the response rate was 26%, PFS was 3.2 months (95% confidence interval [CI] 2.7–4.5), and OS was 13.5 months (95% CI 9.4–15.6); the rate of rapid progression (within 2 months) was lower (36%) than that reported in the EGFR (44.8%), ALK (45.5%), or ROS1 (42.9%) populations [12].

The aim of our study was to retrospectively evaluate the impact of KRAS mutations on response and survival outcomes in advanced nonsquamous NSCLC patients treated with ICIs alone or in combination with chemotherapy.

2 Methods

2.1 Patients and Methods

We conducted a retrospective cohort study, analyzing a consecutive series of patients with a histological diagnosis of advanced non-squamous NSCLC and known KRAS mutational status who had received at least one cycle of ICI therapy (atezolizumab, pembrolizumab or nivolumab) at Santa Chiara Hospital, Trento, from March 2017 to August 2021. Patients could receive immunotherapy alone or in combination with chemotherapy in any line of treatment, according to daily clinical practice, and had to have a minimum follow-up of 6 months. KRAS mutations were tested by diagnostic methods available at our Institute (sequenom, real time PCR, next-generation sequencing), while PD-L1 expression levels were analyzed on tumour cells by immunohistochemistry, according to the currently used assay.

We collected the following baseline patient characteristics from the clinical records: sex, date of metastatic disease diagnosis, age at diagnosis, smoking status, number of comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, histologic subtype, stage, number and type of metastatic sites, and biomolecular phenotype, including PD-L1 expression levels and mutational status of EGFR/ALK/ROS1/KRAS/BRAF/other genes.

The following data on ICI-based treatment were collected: type of ICI (atezolizumab, pembrolizumab or nivolumab), possible concomitant administration of chemotherapy, date of first administration, best response to treatment, date and reason of progression/discontinuation, number of cycles received, palliative radiotherapy treatments, and subsequent lines of treatment. Patients were radiologically monitored according to local clinical practice. The response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Lastly, vital status (alive or dead) and date of death/last follow-up were collected.

This study was approved by the APSS Ethical Committee, Trento.

2.2 Statistical Analysis

Descriptive statistics were used to report patient characteristics: median with interquartile range was used to report

continuous variables, and frequency (percentage) was used for categorical variables.

OS was calculated from the date of metastatic disease diagnosis until death due to any cause or the date of the last follow-up for censored patients. In patients receiving an ICI as first line, PFS was calculated from the date of metastatic disease diagnosis until disease progression or death due to any cause or the date of the last follow-up for censored patients; in patients receiving an ICI as a subsequent line of treatment, PFS was calculated from the date of disease progression to previous treatment until disease progression or death due to any cause or the date of the last follow-up for censored patients.

Disease control rate (DCR) was defined as the sum of complete response rate, partial response rate, and stable disease rate.

Kaplan–Meier survival curves were used to estimate median OS and PFS, including 95% CI, and stratified by KRAS mutational status (mutated vs. wild type). Differences were tested via the log-rank test. A Cox proportional hazards model was used to develop multivariable prediction models for OS and PFS. A backward variable selection method with a type I error criterion of 0.05 was used to select factors significantly affecting PFS and OS. An exploratory analysis was performed among mutated patients to investigate the impact of specific KRAS mutations on response and survival outcomes. Statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) [13].

3 Results

We identified a consecutive series of 119 patients treated with an ICI alone or in combination with chemotherapy from March 2017 to August 2021 at Santa Chiara Hospital, Trento.

Baseline patient characteristics are shown in Table 1. Most patients were male (65.5%) and a current or former smoker (84.1%) with adenocarcinoma (89.9%) in stage IV (100%). All were tested for KRAS mutations, with a result of wild type or mutated in 69 and 50 patients, respectively. In the overall population, the median follow-up was 10.3 months (range 0.6–57.3). The median duration of the immunotherapy treatment was 6.2 months (range 0.3–57.3).

No statistically significant difference in OS was found between wild type and mutated KRAS patients: median OS was 14.9 months (95% CI 7.6–22.7) in wild-type KRAS patients versus 14.7 months (95% CI 8.0–19.5) in mutated KRAS patients; $p = 0.529$ (Fig. 1). Similarly, no statistically significant differences in terms of PFS were reported: median PFS was 7.2 months (95% CI 3.5–14.5) in wild-type KRAS patients versus 8.8 months (95% CI 4.4–14.7) in mutated KRAS patients; $p = 0.768$ (Fig. 2). The DCR was 55% and 64% in the wild type and mutated KRAS groups, respectively. This confirmed that the control rate was not significantly associated with KRAS status ($p = 0.642$) (Table 2).

At multivariable analysis, brain metastases (HR 2.11, 95% CI 1.29–3.45; $p = 0.002$) and nivolumab treatment (0.36, 95% CI 0.16–0.79; $p = 0.011$) were independently associated with OS, while brain metastases (2.14, 95% CI 1.31–3.51; $p = 0.002$) and immune-chemotherapy treatment (0.40, 95% CI 0.19–0.85; $p = 0.017$) were independently associated with PFS (Table 3). Patients with brain involvement reported a significantly shorter OS and PFS, while those treated with immunotherapy plus chemotherapy reported a significantly longer PFS.

No statistically significant difference was found in terms of PFS and OS between patients with PS 0 or PS 2, which was likely due to the small number of patients with PS 2 (only 4) versus PS 0 (92).

We collected the KRAS mutation subtypes and evaluated their impact on survival. Among mutated KRAS patients, 26 (52%) had p.G12C, while 24 (48%) patients had other mutations (p.G12A, p.G12D, p.G12S, p.G12V, p.G13D, pQ61H, pQ61L). Median OS was 11 months (95% CI 5.6–19.5) in KRAS G12C patients versus 17 months (95% CI 6.3–31.1) in patients with other KRAS mutations; $p = 0.448$ (Fig. 3). Median PFS was 6 months (95% CI 3.7–14.6) in KRAS G12C patients versus 11 months (95% CI 3.9–17) in patients with other KRAS mutations; $p = 0.609$ (Fig. 4). DCR was similar between the two groups: 61.5% in the KRAS G12C group versus 66.7% in the other mutation groups ($p = 0.912$).

Data on subsequent treatments were not reported, however no patient had ever received a specific KRAS inhibitor because this class of drugs was not available at our institute during the time the patients were treated.

4 Discussion

This study investigated the prognostic role of KRAS mutational status in advanced NSCLC patients treated with an ICI alone or combined with chemotherapy. After a median follow-up of 10.3 months, we did not find any differences between wild type and mutated KRAS patients in terms of survival or response outcomes; OS, PFS and DCR were similar between the two groups.

Several meta-analyses have been performed on this topic, leading to conflicting results; two of these meta-analyses failed to demonstrate an impact of KRAS mutational status on survival of NSCLC patients treated with ICIs [14, 15]. More recently, another meta-analysis was performed on six studies, which compared an anti-PD-(L)1 with or

Table 1 Baseline patient characteristics according to KRAS mutational status

	All	KRAS wild type	KRAS mutated	*p*-value
Number of patients	119	69	50	
Age at diagnosis, years [median (IQR)]	68 (62–73)	68 (61–73)	68 (62–73)	0.779
Number of comorbidities [median (IQR)]	2 (1–3)	2 (1–4)	2 (1–3)	0.226
Sex				0.244
Male	78 (65.5)	42 (60.9)	36 (72)	
Female	41 (34.5)	27 (39.1)	14 (28)	
Smoking status				0.397
Never	15 (12.6)	11 (15.9)	4 (8)	
Former	54 (45.4)	32 (46.4)	22 (44)	
Current	46 (38.7)	23 (33.3)	23 (46)	
Unknown	4 (3.4)	3 (4.3)	1 (2)	
ECOG PS				0.934
0	92 (77.3)	53 (76.8)	39 (78.0)	
1	23 (19.3)	14 (20.3)	9 (18.0)	
2	4 (3.4)	2 (2.9)	2 (4.0)	
Stage				
IV	119 (100)	69 (100)	50 (100)	
Histology				0.556
Adenocarcinoma	107 (89.9)	63 (91.3)	44 (88)	
NSCLC—other	12 (10.1)	6 (8.7)	6 (12)	
PD-L1				0.583
< 1%	27 (22.7)	18 (26.1)	9 (18.0)	
1–49%	20 (16.8)	11 (15.9)	9 (18.0)	
≥ 50%	57 (47.9)	30 (43.5)	27 (54.0)	
Unknown	15 (12.6)	10 (14.5)	5 (10.0)	
EGFR				
Wild type	118 (99.2)	68 (98.6)	50 (100)	1.000
Mutated	1 (0.8)	1 (1.4)	0 (0)	
ALK				
Wild type	110 (92.4)	66 (95.7)	44 (88.0)	0.068
Mutated	1 (0.8)	1 (1.4)	0 (0.0)	
Unknown	8 (6.7)	2 (2.9)	6 (12.0)	
ROS1				0.556
Wild type	107 (89.9)	63 (91.3)	44 (88.0)	
Unknown	12 (10.1)	6 (8.7)	6 (12.0)	
KRAS subtype				< 0.001
Wild type	69 (58.0)	69 (100)	0 (0)	
p.G12C	26 (21.8)	0 (0)	26 (52.0)	
p.G12A	3 (2.5)	0 (0)	3 (6.0)	
p.G12D	4 (3.4)	0 (0)	4 (8.0)	
p.G12S	4 (3.4)	0 (0)	4 (8.0)	
p.G12V	7 (5.9)	0 (0)	7 (14.0)	
p.G13D	2 (1.7)	0 (0)	2 (4.0)	
p.Q61H	2 (1.7)	0 (0)	2 (4.0)	
p.Q61L	2 (1.7)	0 (0)	2 (4.0)	
Other mutations				0.117
No	108 (90.8)	60 (87)	48 (96)	
Yes	11 (9.2)	9 (13)	2 (4)	
Number of metastatic sites [median (IQR)]	2 (1–3)	2 (1–3)	2 (1–2)	0.243

Table 1 (continued)

	All	KRAS wild type	KRAS mutated	*p*-value
Visceral metastases				0.690
No	36 (30.3)	22 (31.9)	14 (28.0)	
Yes	83 (69.7)	47 (68.1)	36 (72.0)	
Brain metastases, %				1.000
No	91 (76.5)	53 (76.8)	38 (76.0)	
Yes	28 (23.5)	16 (23.2)	12 (24.0)	
Liver metastases, %				1.000
No	104 (87.4)	60 (87.0)	44 (88.0)	
Yes	15 (12.6)	9 (13.0)	6 (12.0)	
Drug				0.161
Atezolizumab	16 (13.4)	8 (11.6)	8 (16.0)	
Pembrolizumab	82 (68.9)	45 (65.2)	37 (74.0)	
Nivolumab	21 (17.6)	16 (23.2)	5 (10.0)	
Line of treatment				0.109
1L	79 (66.4)	43 (62.3)	36 (72.0)	
2L	25 (21.0)	13 (18.8)	12 (24.0)	
3L	10 (8.4)	9 (13.0)	1 (2.0)	
4L	5 (4.2)	4 (5.8)	1 (2.0)	
Mono/combination therapy				0.824
Monotherapy	94 (79.0)	55 (79.7)	39 (78.0)	
Combination therapy	25 (21.0)	14 (20.3)	11 (22.0)	
Radiotherapy				1.000
No	82 (68.9)	48 (69.6)	34 (68.0)	
Yes	37 (31.1)	21 (30.4)	16 (32.0)	

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *ECOG PS* Eastern Cooperative Oncology Group performance status, *NSCLC* non-small cell lung cancer, *PD-L1* programmed death-ligand 1, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase

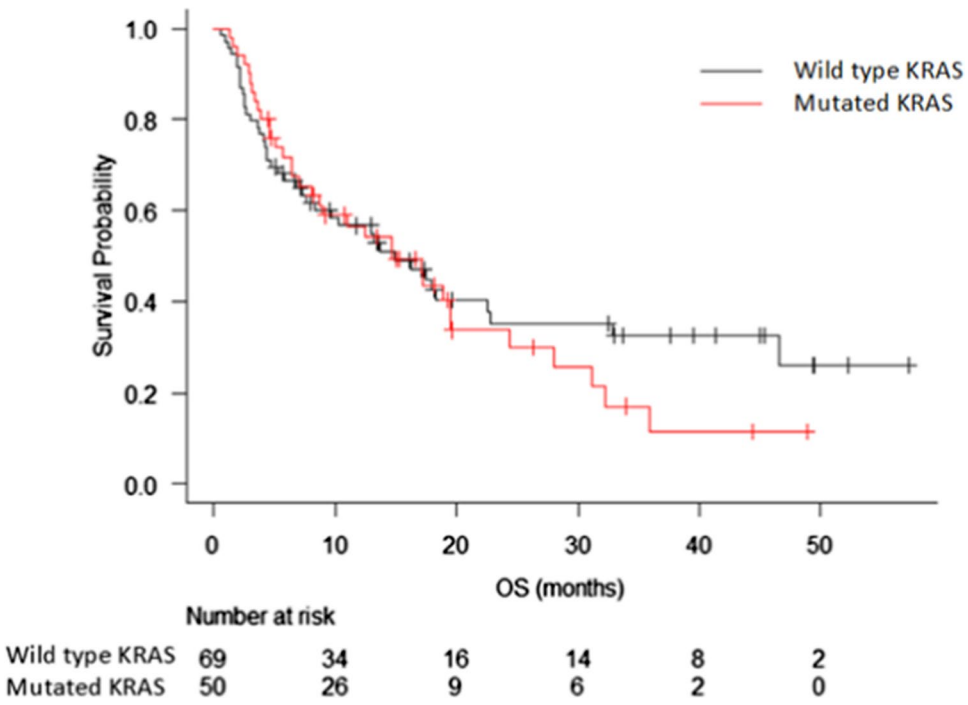

Fig. 1 OS according to KRAS mutational status. *OS* overall survival

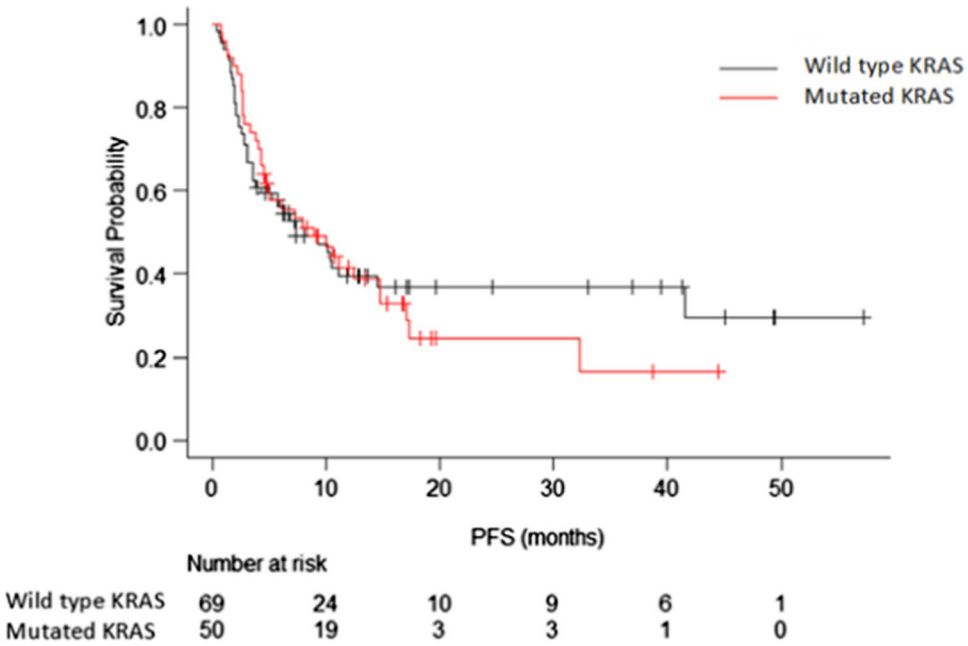

Fig. 2 PFS according to KRAS mutational status. *PFS* progression-free survival

Table 2 Best response assessment by KRAS mutational status

	All	KRAS wild type	KRAS mutated	*p*-value
	119	69	50	
Best response				0.642
PR	44 (37.0)	25 (36.2)	19 (38.0)	
SD	20 (16.8)	9 (13.0)	11 (22.0)	
CR	6 (5.0)	4 (5.8)	2 (4.0)	
PD	38 (31.9)	23 (33.3)	15 (30.0)	
NE	11 (9.2)	8 (11.6)	3 (6.0)	
DCR	70 (58.8)	38 (55)	32 (64)	

Data are expressed as *n* (%)

PR partial response, *SD* stable disease, *CR* complete response, *PD* progression disease, *NE* not evaluated, *DCR* CR+PR+SD

without chemotherapy and chemotherapy alone. The authors found that in 386 KRAS-mutant patients, anti-PD-(L)1 plus chemotherapy prolonged OS (HR 0.59, 95% CI 0.49–0.72; $p < 0.00001$) compared with chemotherapy alone, regardless of the treatment line. Moreover, OS was significantly longer in mutated KRAS patients than wild-type KRAS patients ($p = 0.001$) [16]. Finally, a meta-analysis regarding the activity of ICIs in oncogene-addicted NSCLC patients did not demonstrate significant differences in terms of the response rate between mutated and wild-type KRAS patients (odds ratio 1.54, 95% CI 0.81–2.92; $p = 0.19$) [17].

Some real-world retrospective studies tried to clarify the role of KRAS status in NSCLC patients treated with ICIs, again with conflicting results. A Swiss study including 38 patients treated with nivolumab, pembrolizumab or atezolizumab retrospectively reported the efficacy of immunotherapy in mutant KRAS NSCLC patients. DCR, PFS and OS were higher in mutant patients than in wild-type patients: 81% vs. 71%, 13.6 vs. 11.3 months, and 18.5 vs. 17.7 months, respectively [18]. Conversely, another retrospective study did not detect differences in terms of PFS (4.6 vs. 3.3 months; $p = 0.58$) and OS (8.1 vs. 13 months; $p = 0.38$) between 43 mutant KRAS and 117 non-matched wild-type KRAS NSCLC patients treated with ICIs. At multivariate analysis, only ECOG PS 2 was associated with a higher risk of death (HR 3.14, 95% CI 1.42–6.92; $p = 0.005$) [19]. Similarly, also the largest real-world retrospective study on advanced lung adenocarcinoma patients receiving first-line pembrolizumab failed to confirm an impact of KRAS status on OS (HR 1.03, 95% CI 0.83–1.29), reporting similar survival outcomes between wild-type and mutant KRAS patients (the latter representing 57% of 595 patients) [20].

Our results are in line with those discussed shown: wild-type and mutated KRAS patients demonstrated similar results in terms of OS (14.9 months vs. 14.7 months; $p = 0.529$), PFS (7.2 months vs. 8.8 months; $p = 0.768$) and DCR (55% and 64%; $p = 0.642$).

In our study, at multivariable analysis, brain metastases were independently associated with survival, showing a significantly shorter OS and PFS, likely due to unfavourable prognosis of this subgroup of patients. Instead, patients treated with immunotherapy plus chemotherapy reported a significantly longer PFS, likely related to higher efficacy of combination treatment in mutated KRAS patients.

We also performed a subgroup analysis to explore the impact of KRAS mutation subtype on response and survival outcomes of patients with advanced NSCLC receiving

Table 3 Multivariable analysis for progression-free survival and overall survival

Variable	PFS		OS	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex				
Male	1		1	
Female	0.90 (0.50–1.61)	0.733	0.84 (0.47–1.51)	0.570
ECOG PS				
0	1		1	
1	1.62 (0.87–3.01)	0.124	1.93 (1.04–3.57)	0.035
2	1.27	0.801	1.14 (0.14–8.89)	0.897
Smoking status				
Never	1		1	
Former	1.18 (0.50–2.77)	0.703	0.93 (0.40–2.17)	0.883
Current	0.78 (0.34–1.78)	0.562	0.64 (0.28–1.47)	0.299
Unknown	0.66 (0.07–5.71)	0.709	0.45 (0.04–4.80)	0.516
PD-L1 status				
< 1%	1		1	
1–49%	0.83 (0.31–2.19)	0.717	0.98 (0.38–2.48)	0.971
≥ 50%	0.23 (0.04–1.15)	0.073	0.30 (0.06–1.42)	0.130
Unknown	0.58 (0.17–1.99)	0.390	0.97 (0.28–3.28)	0.963
KRAS status				
Wild type	1		1	
Mutated	1.19 (0.72–1.98)	0.487	1.15 (0.69–1.93)	0.580
Brain metastases				
No	1		1	
Yes	2.38 (1.32–4.30)	0.003	2.59 (1.41–4.73)	0.001
Liver metastases				
No	1		1	
Yes	1.79 (0.82–3.94)		1.80 (0.80–4.04)	0.150
Mono/combination therapy				
Monotherapy	1		1	
Combination therapy	0.10 (0.02–0.49)	0.004	0.17 (0.03–0.76)	0.020
Drug				
Atezolizumab	1		1	
Pembrolizumab	2.08 (0.49–8.69)	0.314	1.98 (0.49–8.00)	0.336
Nivolumab	0.64 (0.22–1.85)	0.418	0.38 (0.12–1.14)	0.084
RT				
No	1		1	
Yes	1.08 (0.61–1.91)	0.771	1.15 (0.64–2.05)	0.632

Hazard ratios with 95% confidence intervals and *p*-values obtained from the Cox regression model

PFS progression-free survival, *OS* overall survival, *ECOS PS* Eastern Cooperative Oncology Group performance status, *PD-L1* programmed death-ligand 1, *RT* radiotherapy

immunotherapy. We found no statistically significant difference in OS, PFS, or DCR between patients with pG12C mutations and those with other KRAS mutations, confirming previously published data [19]. Results from the literature were in line with our results on the prognostic role of KRAS subtypes. In the IMMUNOTARGET study, PFS was not significantly different between KRAS mutation subtypes: G12C versus other KRAS mutations ($p = 0.47$); and G12D versus other KRAS mutations ($p = 0.40$). PFS also was independent of the type of alteration: 2.9 months for transition versus 4.0 months for transversion ($p = 0.27$). PFS did not show a correlation with smoking or number of previous lines of treatment [12]. On the contrary, the Swiss study found that the PFS in the G12C subgroup was longer (19.1 months)

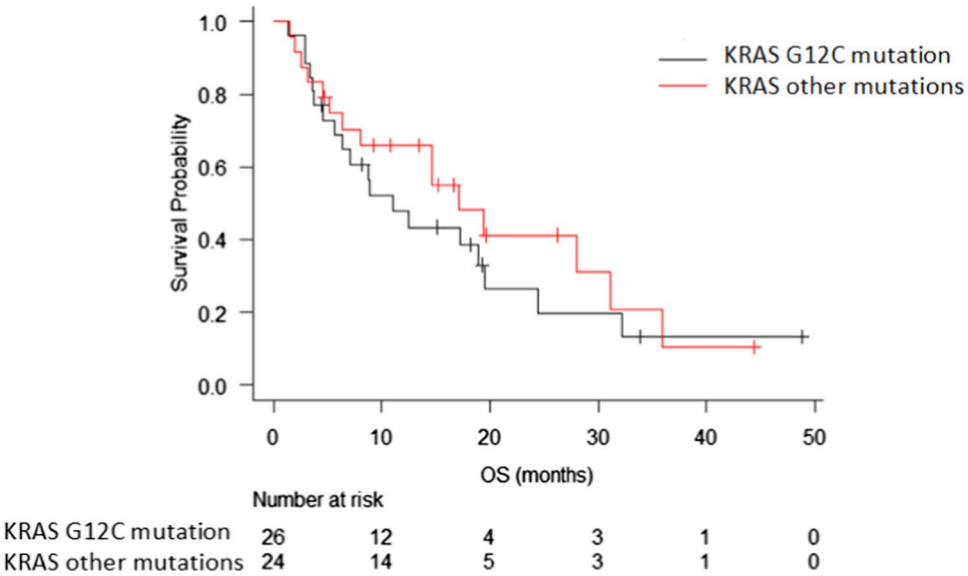

Fig. 3 OS according to KRAS mutation subtype. *OS* overall survival

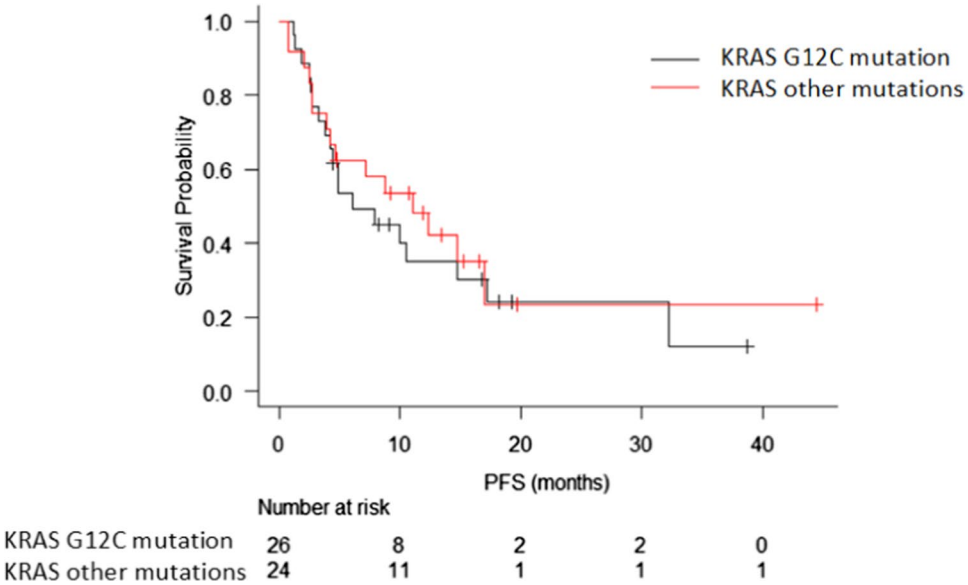

Fig. 4 PFS according to KRAS mutation subtype. *PFS* progression-free survival

than in other KRAS mutation subtypes (7.8, 9.4, 2.2 and 13.9 months for G13C, G12V, G61H, and other mutations, respectively) [18].

The negative prognostic role of KRAS G12C mutation has also been confirmed in 1014 surgically resected stage I–III lung cancers [21].

The largest retrospective observational study on KRAS mutations identified 743 G12C mutated patients among 7069 patients with advanced NSCLC; survival outcomes were independent of G12C mutations and STK11/KEAP1 co-mutations, which were associated with poorer prognosis [22]. Data in the literature are conflicting in regard to the impact of co-mutations on response to immunotherapy in KRAS patients. Mutated KRAS and TP53 patients were found to better respond to immunotherapy [6, 10, 11], while the co-mutations STK11 and KEAP1, detected in about 7% and 23% of KRAS-mutated patients, respectively, are associated with resistance to immunotherapy [1, 6, 10, 18]. In our study, co-mutations were identified in only 11 patients, which we considered too small a subgroup to perform any analysis of their impact on response and survival outcomes.

The detection of KRAS G12C mutation has become important after the introduction of sotorasib, an irreversible inhibitor of KRAS. Promising activity in heavily pretreated lung cancer patients harboring KRAS G12C was reported in a phase I study published in 2020 [23]. The subsequent phase II trial confirmed its efficacy in patients previously treated with both platinum-based chemotherapy and ICIs: the DCR was 80.6%; the median PFS and OS were 6.8 and 12.5 months, respectively; and G3-4 treatment-related

events were 20.6% [24]. The ongoing phase III trial comparing sotorasib with docetaxel will better define the role of sotorasib in the treatment algorithm of KRAS G12C-mutated NSCLC patients (ClinicalTrials.gov identifier: NCT04303780) [25]. Other KRAS inhibitors are being investigated to target KRAS G12C, alone or in combination with chemotherapy or targeted therapies, in order to prevent or delay the development of resistance mechanisms [26].

Our study has some limitations related to the retrospective nature of our research. First, we identified a percentage of KRAS-mutated patients (42%) that is higher than that reported in the literature (about 30%) as well as historically in our institute, where the number of KRAS-mutated patients was generally about 35%. Second, the study population was quite heterogeneous in terms of administered drug and line of treatment; most of the patients (68.9%) received pembrolizumab as first-line treatment, alone or combined with chemotherapy. Third, a longer follow-up and mature OS data are needed to confirm that mutated KRAS patients receiving immunotherapy plus chemotherapy may report a significantly longer survival. Finally, we did not analyse the impact of co-mutations on survival outcomes because they were detected only in 11 patients.

5 Conclusion

Our study confirmed that KRAS mutational status does not negatively impact survival and response outcomes of patients wih advanced non-squamous NSCLC receiving an ICI alone or in combination with chemotherapy. Although previously published data on the prognostic role of KRAS are conflicting, KRAS may not be considered a predictive biomarker of response to immunotherapy.

Declarations

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Conflict of Interest Antonello Veccia, Mariachiara Dipasquale, Stefania Kinspergher, Sara Monteverdi, Salvatore Girlando, Mattia Barbareschi, and Orazio Caffo declare they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval This study was approved by the Ethical Committee of APSS, Trento.

Consent to Participate Not applicable due to the retrospective nature of the study.

Consent for Publication All authors gave their consent for publication.

Availability of Data and Material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Author Contributions AV and OC contributed to the study conception and design, and material preparation, data collection and analysis. The first draft of the manuscript was written by AV and OC, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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