Impact of KRAS mutations on clinical outcomes of patients with advanced non-squamous non-small cell lung cancer receiving anti PD1/PDL1 therapy.

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Abstract

Purpose

To evaluate the impact of KRAS mutations on response and survival outcomes in mutated vs wild type KRAS advanced non squamous non small cell lung cancer patients treated with immune checkpoint inhibitors alone or in combination with chemotherapy.

Patients and methods

We retrospectively identified 119 patients, most of which (58%) were 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 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% CI 7.6 – 22.7) in wild type KRAS patients vs 14.7 months (95% CI 8.0 – 19.5) in mutated KRAS patients; p-value=0.529. No differences were also detected between two groups in terms of PFS and DCR. Patients with pG12C KRAS 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 to chemotherapy.

Introduction

In last years, the prognosis of patients with non small cell lung cancer (NSCLC) significantly improved due to the availability of molecular diagnostics, able to identify aberrations in oncogenes as EGFR, ALK, ROS1, BRAF, and MET, which can benefit by target agents. Among the oncogene alterations identified in NSCLC, Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most frequently altered gene, accounting for approximately 30% of non squamous NSCLC. It encodes an intracellalur protein belonging to guanosine triphosphate (GTP) binding proteins family and it is responsible for the control of cellular signaling transduction and regulation of cell proliferation. After GTP binds to mutated KRAS protein, its constitutive activation triggers the downstream effectors including EGFR, Raf, MEK, PI3K and Akt, leading to uncontrolled tumor cell proliferation and survival *(Yang et al. 2019; Nagasaka et al. 2020; Xie et al. 2021).* KRAS mutations are missense and consist on amino acid changes in codons 12, 13 or 61. The most common is due to change from glycine to cysteine in codon 12 (G12C), that is detected in 13% of lung cancers; others are G12A, G12D, G12R, G12V, G13D, Q61L, and Q61H *(Hunter et al. 2015; Biernacka*

et al. 2016). Besides, KRAS G12C and G12V are more common in smokers, while G12D in former or not smokers *(Davis et al. 2021).*

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.

Anyway, chemotherapy and immunotherapy represent two valid options to be used in this subgroup of patients, who often are smokers and with a higher PDL1 expression levels *(Lan et al. 2018; Ng et al. 2019).* Moreover, genomic analyses showed that KRAS tumors are heterogeneous because of the co-occurring alterations as TP53, CDKN2A/2B, STK11 and KEAP1, that give the tumor different biological properties and therapeutic vulnerability *(Yang et al. 2019; Ghimessy et al. 2020; Davis et al. 2021; Gu et al. 2021).* For example, the 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 PDL1, resulting in a more response to immunotherapy *(Liu et al. 2020; Davis et al. 2021).* All these factors represent a strong biological rationale to explain the interaction between KRAS mutation and sensitivity to ICIs. In the multicentric retrospective IMMUNOTARGET study, ICIs showed to be more effective in mutated KRAS patients than in other subgroups of oncogene addicted tumors. In 271 Kras mutated patients the response rate was 26%, the PFS was 3.2 months (95% 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 EGFR (44.8%), ALK (45.5%) or ROS1 (42.9%) population *(Mazieres et al. 2019).* These data suggested that mutant KRAS patients may benefit from immune checkpoint inhibitors treatment.

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

Methods

Patients and methods

We conducted a retrospective cohort study, including a consecutive series of patients with a histological diagnosis of advanced non squamous NSCLC and known KRAS mutational status, that had received at least one cycle of immune checkpoint inhibitor (atezolizumab, pembrolizumab or nivolumab) at Santa Chiara Hospital of Trento, from March 2017 to August 2021. The patients might receive immunotherapy alone or in combination with chemotherapy in any line of treatment, according to the daily clinical practice, and had to have a minimum follow-up of 6 months. KRAS mutations were tested by diagnostic method available or more appropriate (sequenom, Real Time - PCR, Next Generation Sequencing), while PDL1 expression levels were analyzed on tumor cells by immunohistochemistry, according to the currently used assay.

We collected from the clinical records the baseline patients' characteristics: sex, date of metastatic disease diagnosis, age at diagnosis, smoking status, number of comorbidities, ECOG performance status,

histologic subtype, stage, number and type of metastatic sites, and biomolecular phenotype, including PDL1 expression levels, and EGFR/ALK/ROS1/KRAS/BRAF/other genes mutational status.

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 the treatment, date and reason of progression/discontinuation, number of cycles received, palliative radiotherapy treatments, subsequent lines of treatment. The patients were radiologically monitored according to the local clinical practice. The response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Finally, vital status (alive or dead) and date of death/last follow-up were collected.

Local ethical committee gave its approval.

Statistical analysis

Descriptive statistics were used to report patients' characteristics: median with interquartile range was used to report continuous variables, frequency (percentage) for categorical variables.

OS was calculated from the date of the first administration of the immune checkpoint inhibitor until death due to any cause or the date of the last follow-up for censored patients. PFS was calculated from the date of the first administration of the immune checkpoint inhibitor until disease progression or death to any cause or the date of the last follow-up for censored patients.

Disease control rate 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% confidence interval (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 with R software (version 4.1.2) *(R Core Team 2021)*.

Results

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

Baseline patients’ characteristics are shown in Table 1.

Table 1
Baseline patients' characteristics according to KRAS mutational status.

	All	KRAS wild type	KRAS mutated	P value
Number of pts	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, n (%)				0.244
Male	78 (65.5)	42 (60.9)	36 (72)	
Female	41 (34.5)	27 (39.1)	14 (28)	
Smoking status, n (%)				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, n (%)				0.934
0, n (%)	92 (77.3)	53 (76.8)	39 (78.0)	
1, n (%)	23 (19.3)	14 (20.3)	9 (18.0)	
2, n (%)	4 (3.4)	2 (2.9)	2 (4.0)	
Stage, n (%)				
IV, n (%)	119 (100)	69 (100)	50 (100)	
Histology, n (%)				0.556
Adenocarcinoma, n (%)	107 (89.9)	63 (91.3)	44 (88)	
NSCLC – other, n (%)	12 (10.1)	6 (8.7)	6 (12)	
PDL1, n (%)				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)	

	All	KRAS wild type	KRAS mutated	P value
unknown	15 (12.6)	10 (14.5)	5 (10.0)	
EGFR, n (%)				
Wild type, n (%)	118 (99.2)	68 (98.6)	50 (100)	1.000
Mutated, n (%)	1 (0.8)	1 (1.4)	0 (0)	
ALK, n (%)				
Wild type, n (%)	110 (92.4)	66 (95.7)	44 (88.0)	0.068
Mutated, n (%)	1 (0.8)	1 (1.4)	0 (0.0)	
Unknown, n (%)	8 (6.7)	2 (2.9)	6 (12.0)	
ROS1, n (%)				0.556
Wild type, n (%)	107 (89.9)	63 (91.3)	44 (88.0)	
Unknown, n (%)	12 (10.1)	6 (8.7)	6 (12.0)	
KRAS subtype, n (%)				< 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, n (%)				0.117
No	108 (90.8)	60 (87)	48 (96)	
Yes	11 (9.2)	9 (13)	2 (4)	
Number of metastatic sites, n median (IQR)	2 (1–3)	2 (1–3)	2 (1–2)	0.243
Visceral metastases, n (%)				0.690
No	36 (30.3)	22 (31.9)	14 (28.0)	

	All	KRAS wild type	KRAS mutated	P value
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)	

Most of the patients were male (65.5%), current or former smoker (84.1%) and with adenocarcinoma (89.9%) in stage IV (100%). All were tested for KRAS mutation, that resulted wild type and 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)

Median OS was 14.9 months (95% CI 7.6–22.7) in wild type KRAS patients vs 14.7 months (95% CI 8.0–19.5) in mutated KRAS patients; p-value = 0.529 (Fig. 1).

Median PFS was 7.2 months (95% CI 3.5–14.5) in wild type KRAS patients vs 8.8 months (95% CI 4.4–14.7) in mutated KRAS patients; p-value = 0.768 (Fig. 2).

Overall, the DCR was 55% and 64% in wild type and mutated KRAS groups, respectively, confirming not to be significantly associated with KRAS status (p = 0.642) (Table 2).

Table 2
Best response assessment by KRAS mutational status.

	All	**KRAS wild type**	**KRAS mutated**	**p-value**
	119	69	50	
Best response n, (%)				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, n (%)	70 (58.8)	38 (55)	32 (64)	

PR = partial response; SD = stable disease; CR = complete response; PD = progression disease; NE = not evaluated; DCR = CR + PR + SD.

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 tretated with immunotherapy plus chemotherapy reported a significantly longer PFS.

Table 3
Multivariable analysis for PFS and OS.

	PFS		OS	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sex				
M	1		1	
F	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
PDL1 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				

Hazard ratio with 95% CI and p-values obtained from Cox regression model.

	PFS		OS	
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 ratio with 95% CI and p-values obtained from Cox regression model.				

Among KRAS mutated patients, 26 (52%) of them had p.G12C mutation 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 G12C KRAS patients vs 17 months (95% CI 6.3–31.1) in other KRAS mutation patients; p-value = 0.448 (Fig. 3).

Median PFS was 6 months (95% CI 3.7–14.6) in G12C KRAS patients vs 11 months (95% CI 3.9–17) in other KRAS mutation patients; p-value = 0.609 (Fig. 4).

Disease control rate was similar between two groups: 61.5% in G12C KRAS group vs 66.7% in other mutations group (p = 0.912).

Discussion

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

Several metanalyses has been performed on this topic, leading to conflicting results.

The first metanalyses failed to demonstrate an impact of KRAS mutational status on survival of NSCLC patients treated with ICI *(Lee et al. 2016; Kim et al. 2017).*

More recently, another metanalysis was performed on six first- and second-line studies which compared an anti-PD-(L)1 with or without chemotherapy to chemotherapy alone: the authors found that in 386 KRAS-mutant patients, the anti-PD-(L)1 plus chemotherapy prolonged OS (HR 0.59 [95% CI, 0.49–0.72]; p < 0.00001) compared to chemotherapy alone, regardless the treatment line; moreover, OS of mutated KRAS was significantly longer than wild type KRAS (p = 0.001) *(Landre et al. 2021).*

Finally, a metanalysis concerning the activity of ICIs in oncogene addicted NSCLC patients did not demonstrate any significant difference in terms of response rate between mutated and wyld type KRAS patients (OR 1.54, 95% CI 0.81–2.92; p = 0.19) *(Guaitoli et al. 2021).*

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. The DCR, PFS and OS were higher in mutant than in wild type patients: 81% vs 71%, 13.6 vs 11.3 months, and 18.5 vs 17.7 months, respectively *(Torralvo et al. 2019).*

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 resulted associated with a higher risk of death (HR = 3.14, 95% CI 1.42–6.92; p = 0.005) *(Gianoncelli et al. 2020)*

Similarly, also the most large real-world retrospective study on advanced lung adenocarcinoma patients receiving with 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) *(Noordhof et al. 2021).*

Our study is in line with these results: wild type and mutated KRAS patients reported similar results in terms of OS (14.9 months vs 14.7 months; p-value = 0.529), PFS (7.2 months vs 8.8 months; p-value = 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, probably due to unfavorable prognosis of this subgroup of patients. Instead, patient 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 advanced NSCLC receiving immunotherapy. We found no statistically

significant differences in OS, PFS and DCR between patients with pG12C mutations and those with other KRAS mutations, confirming other previously reported data (*Gianoncell et al. 2020).*

Data from literature were in line with our results on the prognostic role of KRAS subtypes. In IMMUNOTARGET study, PFS was not significantly different between KRAS mutation subtype: G12C vs other KRAS mutations, p = 0.47; G12D vs other KRAS mutations, p = 0.40. PFS also was independent of type of alteration: 2.9 months for transition vs 4.0 months for transversion; p = 0.27. PFS did not show correlation with smoking or number of previous lines of treatment *(Mazieres et al. 2019*). On the contrary, the Swiss study found that the PFS in G12C subgroup was longer (19.1 months) than in other KRAS mutation subtype (7.8, 9.4, 2.2 and 13.9 months for G13C, G12V, G61H and other mutations, respectively) *(Torralvo et al. 2019).*

The negative prognostic role G12C KRAS mutation was confirmed also in 1014 surgically resected lung cancers with I to III stage *(Finn et al. 2021).*

The largest retrospective observational study on KRAS mutations identified 743 G12C mutated patient among 7069 advanced NSCLC: survival outcomes were independent of G12C mutation and STK11/KEAP1 co-mutations, that resulted associated with poorer prognosis (*Spira et al. 2021).*

Data of literature are conflicting also about the impact of comutations on response to immunotherapy in KRAS patients. Mutated KRAS and TP53 patients were found to better respond to immunotherapy *(Liu et al. 202, Davis et al. 2021; Gu et al. 2021)*, while the comutation STK11 and KEAP1, detected in about 7% and 23% of KRAS mutated patients, respectively, are associated to resistance to immunotherapy *(Yang et al. 2019; Torralvo et al. 2019; Davis et al. 2021; Gu et al. 2021).*

The detection of G12C KRAS mutation has become important after the introduction of sotorasib, an irreversible inhibitor of KRAS, whose promising activity in heavily pretreated lung cancer patients harboring G12C KRAS was reported in a phase 1 study published in 2020 *(Hong et al. 2020)*. The subsequent phase 2 trial confirmed its efficacy in patients previously treated with both platinum based chemotherapy and immune checkpoint inhibitors: 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% *(Skoulidis et al. 2021).* Data from the ongoing phase 3 trial of comparison with docetaxel will better define the role of sotorasib in the treatment algorithm of G12C KRAS mutated NSCLC patients *(*ClinicalTrials.gov Identifier *NCT04303780).* Other KRAS inhibitors are actually being investigated to target G12C KRAS, alone or in combination with chemotherapy or target therapies, in order to prevent or delay the development of resistance mechanisms *(Reck et al. 2021).*

Our study presents some limitations related to retrospective nature of our research. First, we found a percentage of KRAS mutated patients (42%) that is higher than that reported in literature (about 30%). Second, the study population was quite heterogeneous in terms of administered drug and line of treatment: most of the patients (68.9%) received pembrolizumab, mostly as first-line treatment, alone or combined to chemotherapy. Third, a longer follow-up and mature OS data are needed to confirm that

mutated KRAS patients receiving immunotherapy plus chemotherapy reported a significantly longer survival. Finally, we did not analysed the impact of comutations on survival outcomes because they were detected only in 11 patients, preventing a powerful statistical analysis.

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

Declarations

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Antonello Veccia and Orazio Caffo contributed to the study conception and design. Material preparation, data collection and analysis were performed by Antonello Veccia and Orazio Caffo. The first draft of the manuscript was written by Antonello Veccia and Orazio Caffo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

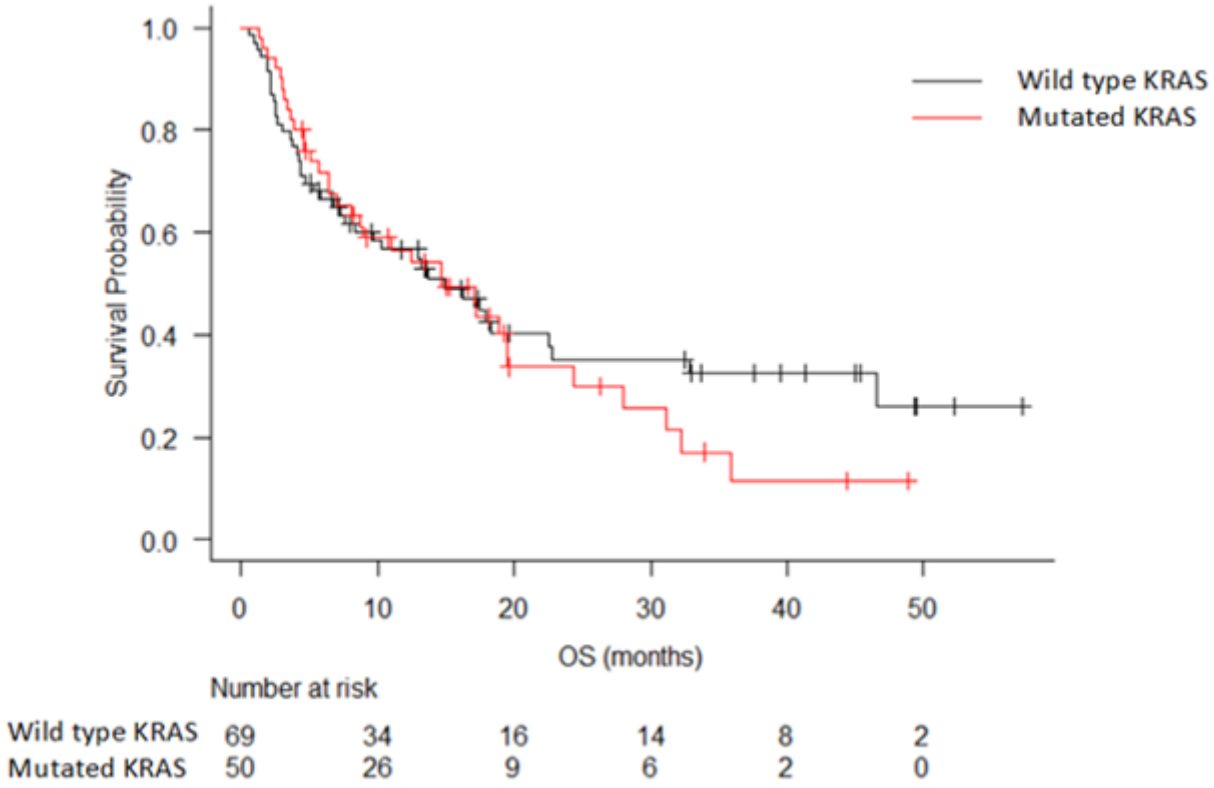

Figure 1

OS according to KRAS mutational status.

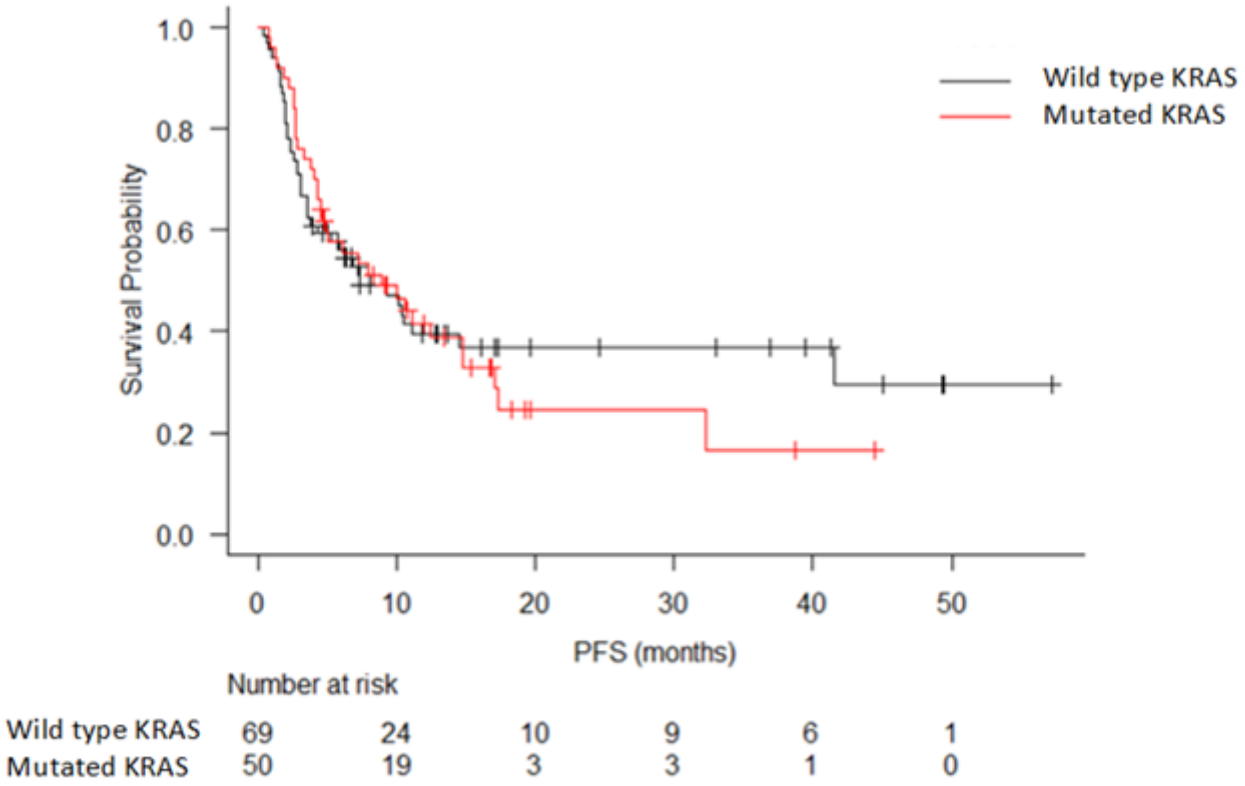

Figure 2

PFS according to KRAS mutational status.

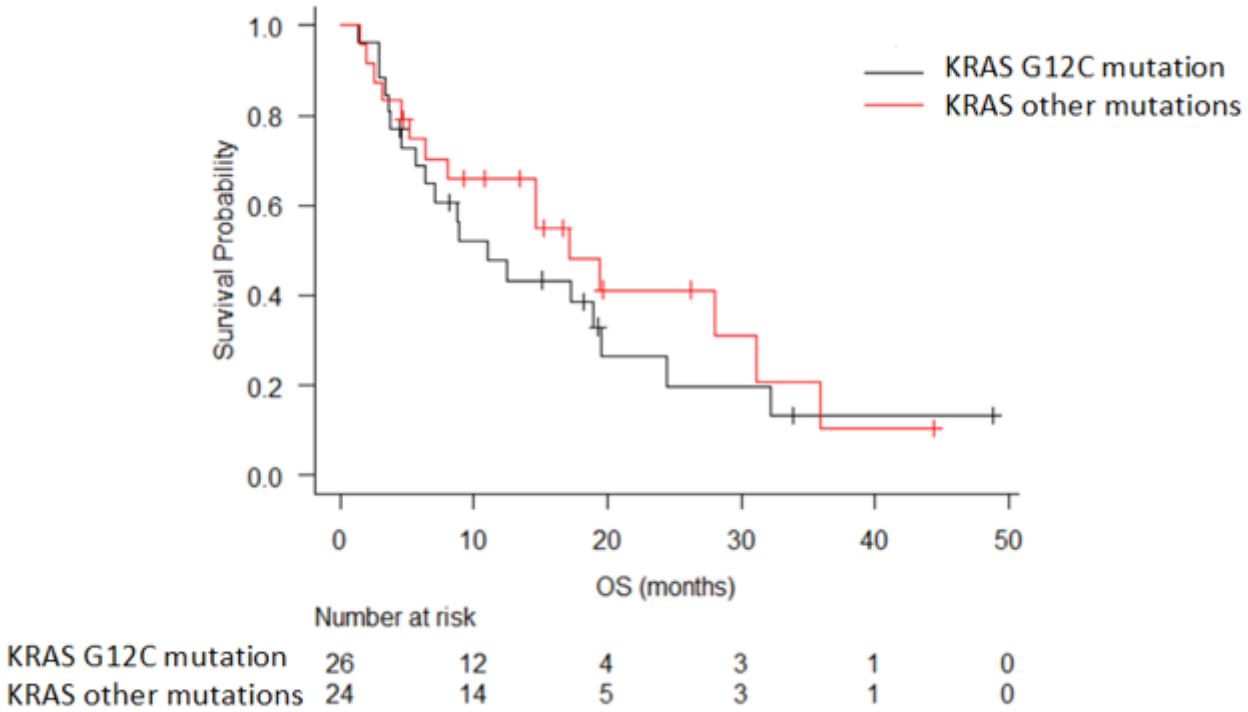

Figure 3

OS according to KRAS mutation subtype.

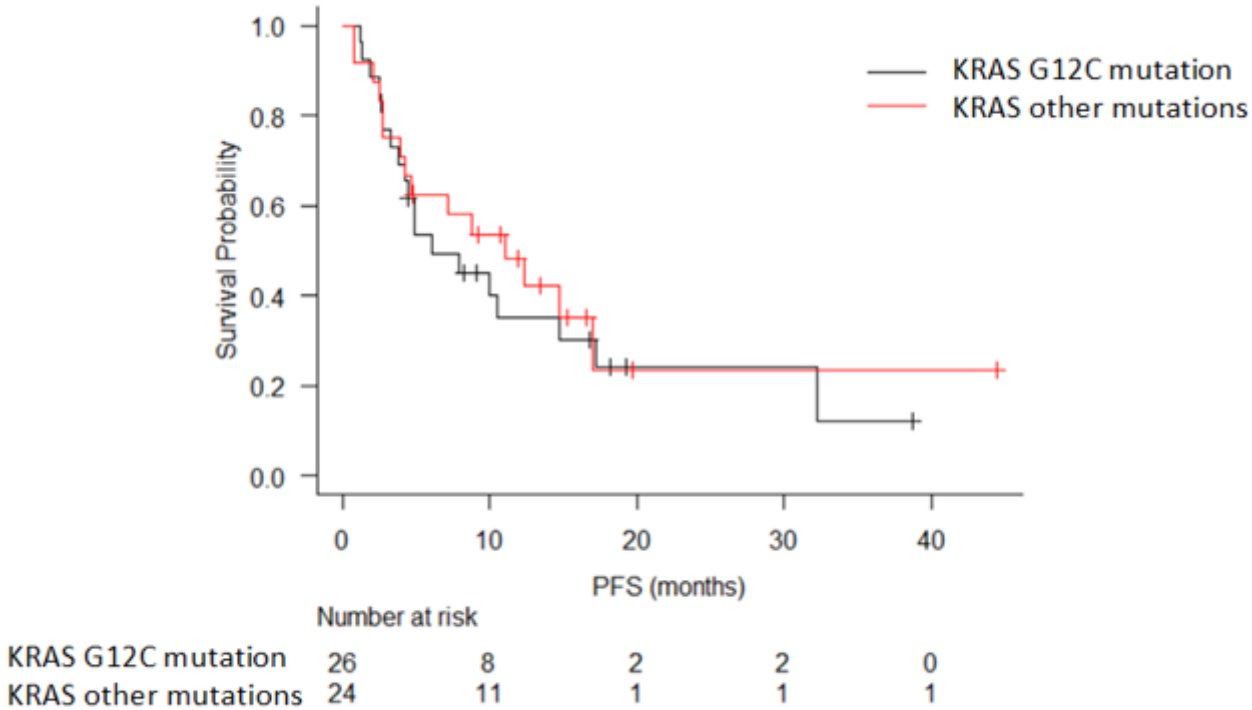

Figure 4

PFS according to KRAS mutation subtype.