Prognostic impact of KRAS variant status in patients with non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitor (ICI) monotherapy

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Background

KRAS gene mutations are found in 20-30% of NSCLC. The prognostic value of KRAS status in NSCLC is still controversial and may be affected by mutation subtypes. Moreover, KRAS mutations have been associated with increased programmed death-ligand 1 (PD-L1) expression, high tumor mutation burden and might be associated with greater benefit from ICI. Therefore, we explored the prognostic impact of KRAS mutations in patients with advanced NSCLC treated with ICI monotherapy.

Methods

We reviewed data of 227 consecutive patients with advanced NSCLC treated with ICI monotherapy at our institution from January 2016 to March 2021. The prognostic impact of KRAS status was investigated through Kaplan-Meier and Cox-regression methods in terms of both progression-free survival (PFS) and overall survival (OS).

No conflicts of interest to declare

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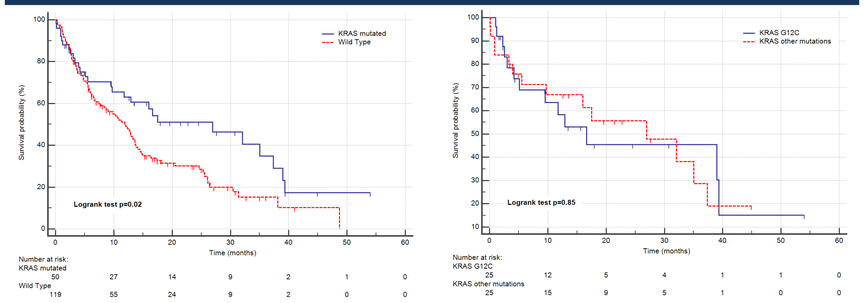
Baseline Patients Characteristics

Subgroup	Whole cohort n=169(%)	KRAS mut n=50	KRAS wt n=119	p
Age >65	108 (63.9)	31	77	0.73
Male sex	105 (62.1)	30	75	0.71
Current/former smoker	141 (83.4)	47	94	0.01
Histology				0.01
Adenocarcinoma	140 (82.8)	48	92	
Squamous	13 (7.7)	1	15	
NOS	16 (9.5)	1	12	
TNM Stage IV	160 (94.7)	48	112	0.61
ECOG PS ≥1	114 (67.4)	30	84	0.23
KRAS mutation	50 (29.6)	50 (100.0)	0	-
Codon 12	44 (26.0)	44		
G12C	25 (14.8)	25		
Codon 13	4 (2.4)	4		
Codon 61	2 (1.2)	2		
Wild type	119 (70.4)	-	119 (100.0)	
Other driver mutations	23 (13.6)	4	19	0.12
PDL1				0.25
0	32 (24.8)	6	26	
1-49%	22 (17.1)	8	14	
≥50%	75 (58.1)	25	50	
Liver localizations	30 (17.8)	7	23	0.40
CNS localizations	39 (23.1)	15	24	0.16
Prior treatments				0.72
No	60 (35.5)	20	40	
Platinum-based CT	102 (60.4)	28	74	
Single-agent CT	7 (4.1)	2	5	
Treatment line >1	105 (62.1)	29	76	0.65

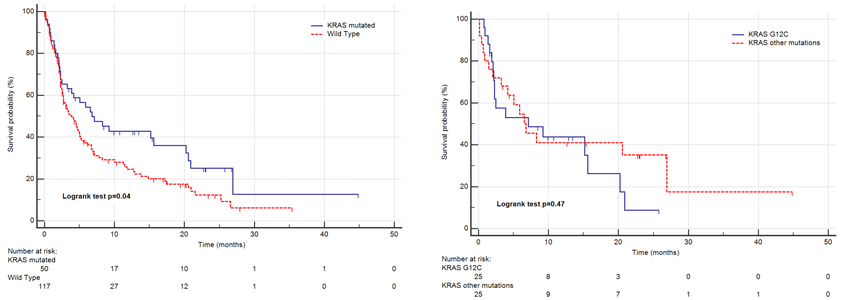
Prognostic impact of KRAS mutations in terms of PFS
Cox proportional hazards regression

Covariates	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p	HR	CI 95%	p
KRAS mutation	0.66	0.44-0.98	0.04	1.39	0.93-2.08	0.10
Age >65	1.30	0.90-1.89	0.15			
Male sex	0.92	0.64-1.31	0.66			
Squamous histology	1.40	0.75-2.60	0.28			
Stage IV	0.79	0.36-1.70	0.55			
ECOG PS ≥1	1.39	0.95-2.03	0.08			
Liver localizations	1.84	1.21-2.79	<0.01	1.95	1.28-2.98	<0.01
CNS localizations	0.89	0.58-1.36	0.61			
Treatment line >1	1.80	1.24-2.62	<0.01	1.87	1.28-2.73	<0.01

Kaplan-Meier analysis in terms of OS



Kaplan-Meier analysis in terms of PFS



Prognostic impact of KRAS mutations in terms of OS
Cox proportional hazards regression

Covariates	Univariate analysis			Multivariate analysis		
	HR	CI 95%	p	HR	CI 95%	p
KRAS mutation	0.60	0.38-0.93	0.02	0.59	0.37-0.94	0.02
Age >65	1.61	1.08-2.40	0.01	1.46	0.96-2.23	0.07
Male sex	1.04	0.71-1.53	0.81			
Squamous histology	1.59	0.85-2.99	0.14			
Stage IV	0.64	0.28-1.48	0.30			
ECOG PS ≥1	2.10	1.37-3.22	<0.001	1.96	1.26-3.04	<0.01
Liver localizations	1.65	1.04-2.61	0.03	1.85	1.15-2.98	0.01
CNS localizations	0.93	0.59-1.47	0.93			
Treatment line >1	1.68	1.12-2.51	0.01	1.82	1.21-2.74	<0.01

Results

Overall, 169 patients with known KRAS variant status were included in the analysis. PD-L1 status was negative in 25% of cases and 58% had a TPS ≥50%. KRAS mutations were identified in about 30% of patients. The most frequent molecular alteration was codon 12 mutation (n=44; 25 patients with KRASG12C mutations). The 38% of patients were treated with ICI monotherapy at first-line and 15% after at least two prior treatment lines. In our cohort, patients with KRAS mutations were found to have better OS (26.94 vs. 12.02 months, HR 0.63, 95% CI 0.42-0.93, p=0.02) and PFS (6.76 vs. 3.84 months, HR 0.68, 95% CI 0.47-0.98, p=0.04) compared with patients without KRAS mutations. In contrast, no difference in terms of OS (HR 1.07, 95% CI 0.50-2.30, p=0.85) and PFS (HR1.29, 95% CI 0.64-2.62, p=0.47) was detected between patients with KRASG12C vs. KRASnon-G12C mutations. The independent prognostic value of KRAS mutations was confirmed through multivariate cox-regression analysis in terms of OS (HR 0.59, 95% IC 0.37-0.94, p=0.02) but not PFS (HR 1.39, 95% CI 0.93-2.08, p=0.10).

Conclusions

KRAS mutations are associated with prolonged survival in patients with NSCLC treated with ICI monotherapy, with no differences according to mutation subtypes.