KRAS G12C lung adenocarcinoma represents a distinct group of patients with different response to immunotherapy

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Background

KRAS mutation is the most common targetable alteration detected in NSCLC (non-small cell lung cancer). *KRAS G12C* mutation accounts for approximately 34% of *KRAS* mutations and recently, Sotorasib and Adagrasib have been approved for the treatment of these patients with promising results. Immunotherapy is currently standard treatment for the majority of NSCLC patients, including those with *KRAS* mutations.

The impact of the different *KRAS* mutations on the response to immunotherapy is being studied, but very little information is yet available.

Objective

We aimed to assess clinical, pathological characteristics, and outcomes on immunotherapy for tumors harboring *KRAS G12C* mutation compared to other *KRAS* mutations.

Methods

Patients with LUADs treated with immunotherapy were prospectively included between January 2017 and July 2020 in our database. Clinicopathological and molecular data were collected and interrogated to evaluate associations between patients' characteristics, treatment response and survival outcomes.

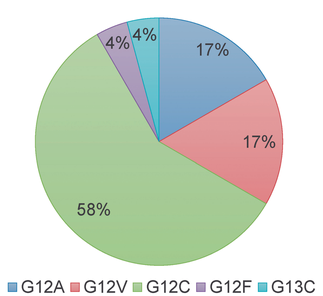

Figure 1. Percentage of different *KRAS* mutations

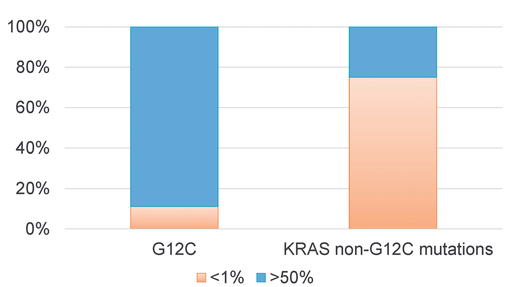

Figure 2. Different PD-L1 expression in relation with *KRAS* mutation

Characteristics (n=89)	n (%)
Age median (range)	64 (range 40-78)
Sex	
Male	70 (78.6)
Female	19 (21.3)
Tobacco	
Never smoker	6 (6.7)
Former smoker	34 (38.2)
Current smoker	49 (55)
Tumor stage (8th Edition)	
I	2 (2.2)
II	7 (7.9)
III	13 (14.6)
IV	67 (75.2)
Molecular Alterations	
No targetable alterations	53 (59.5)
KRAS mutations	24 (26.9)
EGFR mutations	1 (1.1)
MET (amplification or exon skipping)	5 (5.6)
BRAF (Thr599dup, V600E and G469A)	3 (3.3)
RET rearrangement	1 (1.1)
NTRK rearrangement	1 (1.1)
HER2 mutation	1 (1.1)
Tumor PD-L1 %	
<1%	31 (34.8)
1-49%	18 (20.2)
≥50%	31 (34.8)
NA	9 (10.1)
Type of immunotherapy	
Nivolumab	32 (35.9)
Pembrolizumab	36 (40.4)
Atezolizumab	21 (23.6)
Line of treatment	
First	32 (36)
Second	49 (55)
Third	7 (7.9)
Fourth	1 (1.1)

Table 1. Patients' characteristics

Results

A total of 89 patients where included in the study. *KRAS* mutations were detected in 24 patients, with *KRAS G12C* representing 58.3% of all *KRAS* mutations, followed by *KRAS G12A, G12V, G12F* and *G13C* (16.6%, 16.6%, 4.2% and 4.2% respectively). PD-L1≥50% was present in 50% of patients (n=7) with LUADs harboring *KRAS G12C* mutation and in 18.2% (n=2) of patients with *KRAS non-G12C* mutations. Conversely, 16.3% (n=1) of patients harboring *KRAS G12C* mutation was PD-L1 negative compared to 54.5% (n=6) of patients with *KRAS non-G12C* mutations, p=0.036.

Overall response rate to immunotherapy was 31.3% for *KRAS G12C* mutated patients, compared with 18.2% (p=0.65) in other *KRAS* mutations. The median follow-up of this population was 16.6 months. Survival analysis showed a trend towards a better OS in *KRAS G12C* tumors compared with tumors harboring *KRAS non-G12C* mutations (16.3 vs 9.7months, respectively, p=0.34).

Conclusions

LUADs harboring *KRAS G12C* mutations showed higher PD-L1 expression compared to other *KRAS* mutations and may benefit more from immunotherapy. Additional biomarkers might be helpful in selecting the best therapy for patients harboring *KRAS G12C* mutations.

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The authors declare no conflict of interest regarding this work. Contact: *earriola@parcdesalutmar.cat*