

Efficacy of Immune Checkpoint Inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC)

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Brief report: efficacy of immune checkpoint inhibitors in KRAS-mutant Non-small cell lung cancer (NSCLC)

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Abstract

Introduction

KRAS mutation (*KRAS*m) is the most frequent molecular alteration found in advanced non-small cell lung cancer (NSCLC), is associated with a poor prognosis, without available targeted therapy. Treatment options for NSCLC have been recently enriched by the development of immune checkpoint inhibitors (ICI), and data about its efficacy in patients with *KRAS*m NSCLC are discordant. This study assessed the routine efficacy of ICI in advanced *KRAS*m NSCLC.

Methods

In this retrospective study, clinical data were extracted from the medical records of patients with advanced NSCLC treated with ICI and with available molecular analysis between April 2013 and June 2017. Analysis of PD-L1 expression was performed if exploitable tumor material was available.

Results

A total of 282 ICI-treated (in first line or more) advanced NSCLC (all histological subgroups) patients who were treated with ICI (anti-PD-1, anti PD-L1 or anti-CTLA-4 antibodies), including 162 (57.4%) with *KRAS* mutation, 27 (9.6%) with other mutations and 93 (33%) with a wild-type phenotype, were identified. PD-L1 analysis was available for 128 patients (45.4%), of whom 45.3% and 19.5% had PD-L1 expression ≥ 1% and 50%, respectively (49.5% and 21.2% respectively concerning 85 *KRAS*m NSCLC patients).

No significant difference was seen in terms of objective response rates (ORR), progression free survival (PFS) and overall survival (OS) between *KRAS*m NSCLC and other NSCLC. No significant differences in OS or PFS were observed between the major *KRAS* mutation subtypes (G12A, G12C, G12D, G12V, and G13C).

In *KRAS*m NSCLC, unlike in non-*KRAS*m NSCLC, the efficacy of ICI is consistently higher, eventhough not statistically significant, for patients with PD-L1 expression in ≥ 1% of tumor cells than for those with PD-L1 expression in < 1% of tumor cells, and this finding is especially true when PD-L1 expression is high (PD-L1 expression ≥ 50%).

Discussion

For patients with *KRAS*m NSCLC (all mutational subtypes), the efficacy of ICI is similar to that of patients with other types of NSCLC. PD-L1 expression seems to be more relevant for predicting the efficacy of ICI in *KRAS*m NSCLC than it is in other types of NSCLC.

Keywords: NSCLC, immunotherapy, *KRAS* mutation, PD-L1 expression

INTRODUCTION

KRAS mutations are found in approximately 30% of non-small cell lung cancer (NSCLC) (1) and confers a poor prognosis (2). Nevertheless, all studies testing targeted therapies against KRAS and its downstream pathways have failed to show any clinical benefit (3). Current international guidelines recommend a first-line platinum-based treatment for the majority of NSCLC cases, including those harboring a *KRAS* mutation (4).

Immune checkpoint inhibitors (ICI) against PD-1 and PD-L1 inhibitors recently became standard-of-care in second-line treatment for NSCLC (5-7), in first line therapy for highly expressing PD-L1 (8) and will likely become a standard first-line treatment when associated with chemotherapy for all comers NSCLC (9). In clinical trials comparing ICI versus chemotherapy in second-line treatment, a benefit was suggested in patients with *KRAS*-mutated (*KRAS*m) NSCLC (5), based on an unplanned subgroup analysis. More recent data indicate that KRAS-mutated NSCLCs display heterogeneous immune profiles and, consequently, various sensitivity to immunotherapy (10).

Herein, we compared the efficacy of ICI in patients with *KRAS*m NSCLC and other types of NSCLC in a large retrospective cohort of patients routinely treated for NSCLC.

METHODS

1. Population

All patients with metastatic NSCLC who received treatment with ICI between April 2013 and June 2017 at the Assistance Publique-Hôpitaux de Marseille (France) and whose tumor was molecularly characterized were selected. Patients who were treated with ICI for *KRAS*m NSCLC at the University Hospital of Toulouse (France) were also included in this study. Demographic, biological, radiological, therapeutic and survival data were retrospectively collected from the patients' medical records. This study was approved by the national ethics committee *Institutional Review Board of the French Learned Society for Respiratory Medicine - Société de Pneumologie de*

*Langue Française (*CEPRO, Comité d'Evaluation Des Protocoles De Recherche Observationnelle) (approval no. 2016-024, 2017-020 and 2017-043).

2. Molecular analyses

Mutations were investigated in *EGFR, KRAS, BRAF, PIK3CA* and *HER2* in all samples by determining the high-resolution melting point subsequent to polymerase chain reaction (HRM-PCR) profile followed by dideoxy-Sanger sequencing to determine the mutation of interest or by the MiSeq panel (Illumina). *ALK* and *ROS1* rearrangement were detected using an immunohistochemical procedure and positive cases were controlled for by fluorescent in situ hybridization (FISH) (11).

3. PD-L1 expression analyses

When tumor material of an appropriate quality and quantity was available, PD-L1 protein expression (expression in tumor cells) was assessed using immunohistochemistry with a ready-to-use PD-L1 (HD-FG-000035) kit commercial kit (HalioSeek®) or with QR1 antibody (Quartet®) on a Dako Link platform, at pathology platform of Marseille and Toulouse, respectively.

The percentage of tumor cells positive for PD-L1 protein expression was reported. Furthermore, the positivity of the tumors for PD-L1 expression was considered for two thresholds currently used in clinical practice: ≥ 1% or ≥ 50% of positive tumor cells (8).

4. Statistical analyses

The evaluation of tumor response was performed every two months based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (12). Median OS and median PFS were estimated using the Kaplan-Meier method with a confidence interval (CI) of 95%. A Cox model allowed the calculation of hazard ratios (HR) for comparison between different groups with a confidence interval of 95%. A chi-squared test or Fisher's test was used for comparing two quantitative variables, and a Mann-Whitney test was used for comparing means. To compare different groups, odds ratios (OR) were calculated with a statistical regression method with a confidence interval of 95%. Statistical analysis was performed with IBM SPSS version 20.0 for Windows (IBM SPSS Inc., Chicago, IL, United States of America). Statistical significance was declared at the threshold p value of 0.05.

RESULTS

1. Comparison of *KRAS*-mutant NSCLC with other types of NSCLC.

A total of 282 patients were analyzed, of whom 162 had *KRAS*m advanced NSCLC **(figure S1)**. The main characteristics of the population are reported in **table 1**. In total, 273 patients were able to be evaluated for ORR and DCR; 282, for PFS and OS.

The ORR was numerically higher for *KRAS*m NSCLC (18.7%) than for *KRAS* wild-type NSCLC (14.4%), but this difference was not statistically significant (NS). There was no significant difference in terms of PFS or OS **(table 2)**. We also compared the efficacy and toxicity of ICI with respect to *KRAS* mutation subtypes, and no significant difference was observed when patients with G12A (n=15) versus G12C (n=69) versus G12D (n=25) versus G12V (n=24) versus G13C (n=11) mutations were compared **(table 3)**.

2. Analysis of PD-L1 expression

Tumor PD-L1 protein expression was analyzed in 128 patients (45.4%) The mean expression of PD-L1 in different groups was not significantly different even though *KRAS*m NSCLC had a numerically higher expression of PD-L1 than the other groups **(table 4)**. With a cutoff value set at 1%, 49.5% of the tumors of *KRAS*m NSCLC patients were positive for PD-L1 (PD-L1 ≥ 1%) expression, versus 28.6% of the tumors of patients with NSCLC with other mutations and 38.9% of the tumors of patients with wild-type NSCLC. No significant difference was observed between *KRAS*m NSCLC tumors and those of the other groups of NSCLCs.

However, we noted a statistically significant difference in PD-L1 expression between the different subtypes of *KRAS* mutation with a higher proportion of PD-L1 positive tumors in patients with G12D, G12V or G13C *KRAS* mutations and a higher proportion of PD-L1 negative tumors in those with G12A and G12C mutations.

3. Efficacy of ICI with respect to PD-L1 expression.

The ORR, PFS and OS were not significantly different between the different NSCLC groups (with or without *KRAS* mutation) with respect to PD-L1 expression (online

supplemental **table S1**). However, a trend toward a better ORR and a longer PFS was observed for *KRAS*m NSCLC with PD-L1-positive vs PD-L1-negative tumors, with increased benefit for a higher rate of PD-L1 positive tumor cells (≥ 50%) (**figure 1,** panel A). This association between PD-L1 expression and outcome with ICI was not observed in NSCLC without *KRAS* mutations.

We analyzed the association between PD-L1 expression and efficacy of ICI for the different *KRAS* mutation subtypes. No statistically significant association was found (online supplemental **table S2**), but a trend for a positive association between PD-L1 expression and both ORR and PFS with ICI was seen in the groups of patients with G12A or G12V *KRAS* mutations (**figure 1**, panel B).

DISCUSSION

This retrospective study of 282 patients with NSCLC treated with ICI showed that the efficacy, in terms of objective response and survival, of ICI was similar for patients with NSCLC with or without *KRAS* mutation. In the CheckMate 057 study (5), showing a potential advantage for immunotherapy in *KRAS*m NSCLC, the mutation status was unknown for 21% of the patients and only 62 patients (11%) had a known *KRAS* mutation. These data were thus based on a small number of patients and on unplanned subgroup analyses with a potential bias. In our larger cohort that included 162 *KRAS*m NSCLC patients, we did not find any increased benefit for *KRAS*m NSCLC. The proportion of patients with *KRAS*m NSCLC was high in our study (57.4%). The proportion of adenocarcinoma was very high in the current cohort, in which only 2.1% of the patients exhibited squamous histology that rarely harbor *KRAS* mutations. In addition, activating mutations beside *KRAS* mutation were less frequent. It is explained by the fact that targeted therapies, when available, are the standard of care with a lower use of ICI.

In patients with *KRAS*m NSCLC, but not in patients with other NSCLC, a trend for an association between PD-L1 expression in tumor cells and the ORR and PFS was observed, and the benefit increased with the higher threshold for the positivity of the tumors for PD-L1 expression. PD-L1 predicts response to checkpoint inhibitors in the majority of the clinical trials investigating its role in NSCLC (7) (9). However, results are discordant in some trials showing benefits for ICI whatever the PD-L1 status (16).

In addition, its specific role in *KRAS* mutant patients has not been investigated so far. Our data showing the predictivity of PD-L1 expression for ICI efficacy in *KRAS* mutant NSCLC has to be validated in other cohorts. The expression of PD-L1 was found to be significantly different between different subtypes of *KRAS* mutation: a higher proportion of PD-L1-positive tumors was observed in groups with G12D, G12V or G13C *KRAS* mutations, and a higher proportion of PD-L1-negative tumors was observed in those with G12A and G12C mutations. However, because of the small number of patients in each subgroup, these data require validation.

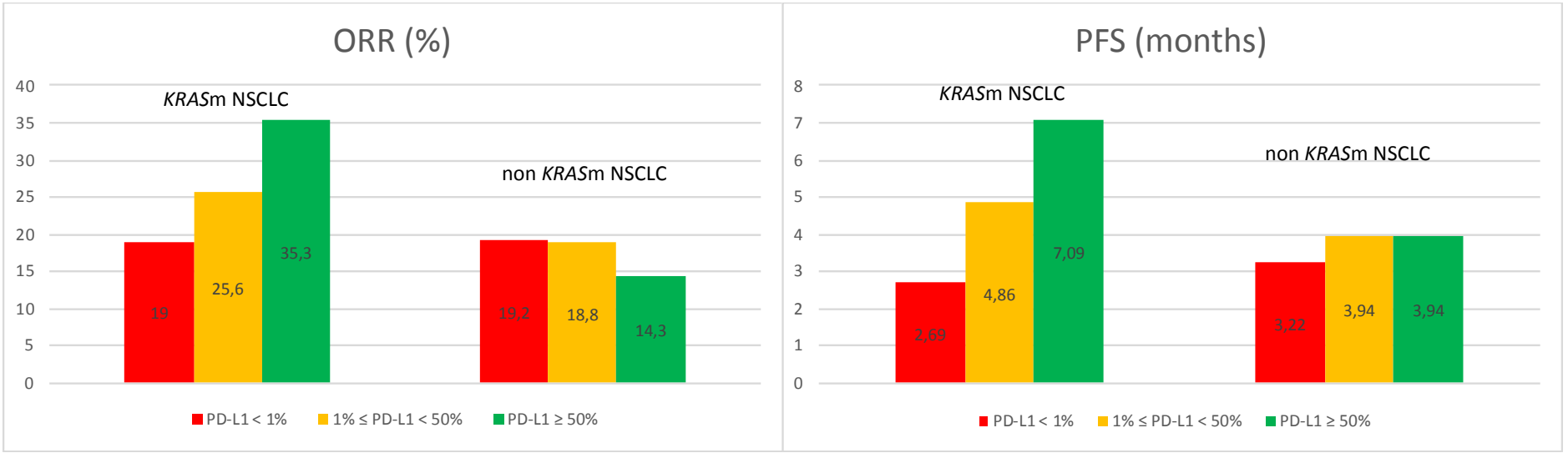
In addition to the different mutation subtypes of *KRAS* and beyond PD-L1 expression, recent data confirm that *KRAS*m NSCLCs are not all equal in terms of the immunogenic profile and response to immunotherapy (10). A group of *KRAS*m lung adenocarcinomas (LUAC), with high rates of *KEAP1* mutational inactivation (“the KL group”), expressed lower rates of expression of immune markers, including PD-L1. In this subgroup, the inactivation of STK11/LKB1 resulted in an accumulation of tumor-associated neutrophils with suppressive effects on T cells and a reduced number of tumor-infiltrating lymphocytes; the KL group is consequently refractory to anti-PD-1 antibody therapy, and other therapeutic strategies that target neutrophils are proposed (13-14). This resistance of *KRAS*m LUAC that lost STK11/LKB1 activity to ICI has been recently clinically confirmed in patients (15).

In conclusion, the clinical benefit of ICI is similar in NSCLC with and without *KRAS* mutation. An association between PD-L1 expression and ICI efficacy was found in *KRAS*m NSCLC. The efficacy of ICI against all mutation types did not seem to be equal, but further validation on larger series of samples is needed. The immunological features of *KRASm* NSCLC and their effect on susceptibility to immunotherapy are thus heterogeneous and are largely underexplored, with the exception of recent studies exploring the KL group. In addition, the combining several immunotherapies or combining immunotherapy with specific targeted therapies or with chemotherapy will thus likely be useful to overcome the resistance of tumors to the PD-L1/PD-1 inhibitors used in monotherapy.

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A.


ORR (%)
KRASm NSCLC
non KRASm NSCLC
19
25,6
35,3
19,2
18,8
14,3
PD-L1 < 1%
1% ≤ PD-L1 < 50%
PD-L1 ≥ 50%
PFS (months)
KRASm NSCLC
non KRASm NSCLC
2,69
4,86
7,09
3,22
3,94
3,94
PD-L1 < 1%
1% ≤ PD-L1 < 50%
PD-L1 ≥ 50%

B.

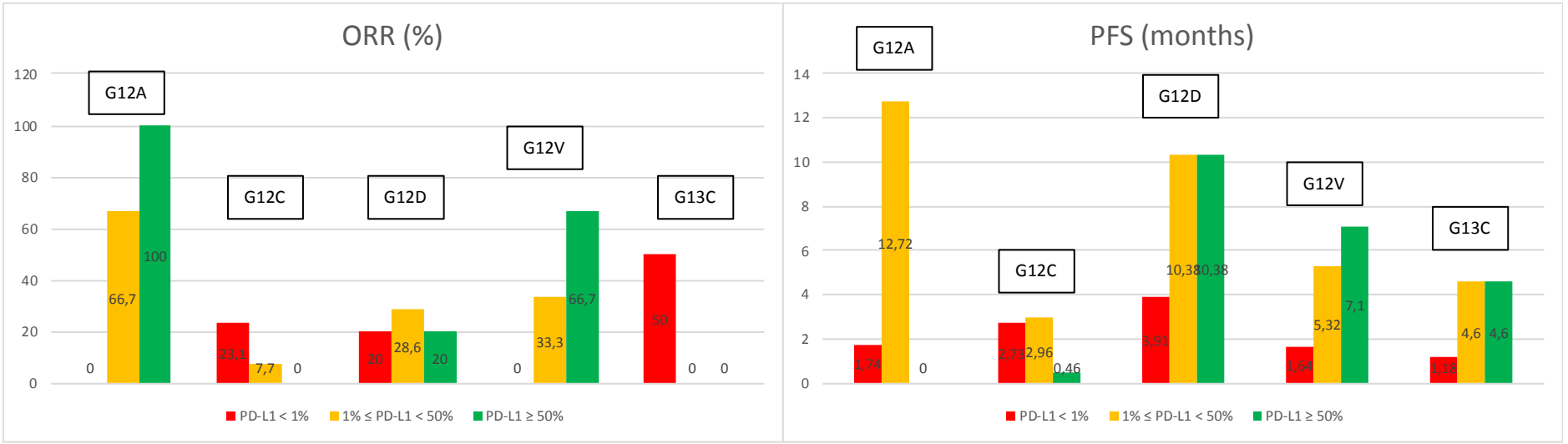

ORR (%)
G12A
G12C
G12D
G12V
G13C
0
66,7
100
23,1
7,7
0
20
28,6
20
0
33,3
66,7
50
0
0
PD-L1 < 1%
1% ≤ PD-L1 < 50%
PD-L1 ≥ 50%
PFS (months)
G12A
G12C
G12D
G12V
G13C
1,74
12,72
0
2,73
2,96
0,46
3,91
10,38
10,38
1,64
5,32
7,1
1,18
4,6
4,6
PD-L1 < 1%
1% ≤ PD-L1 < 50%
PD-L1 ≥ 50%

Figure 1: Association between PD-L1 expression and ICI efficacy:
A. Between *KRAS*m NSCLC and non-*KRAS*m NSCLC.
B. Between the different subtypes of KRAS mutation.

ORR = Overall Response Rate, PFS = Progression-Free Survival, KRAS = Kirsten Rat Sarcoma Virus, PD-L1 = Programmed death ligand 1, OS = Overall Survival

Age at diagnosis - years	
Median	59.8
Range	32-84
Sex - n *(%)*	
Male	168 *(59.5)*
Female	114 *(40.5)*
Smoking status - n *(%)*	
Current smoker	102 *(36.2)*
Former smoker	143 *(50.7)*
Never smoked	25 *(8.9)*
Unknown	1 *(4.2)*
Histology - n *(%)*	
Adenocarcinoma	263 *(93.3)*
Squamous	6 *(2.1)*
Large Cell Carcinoma	9 (3.2)
Other	3 *(1.1)*
Unknown	1 *(0.4)*
PS before ICI - n *(%)*	
0	70 *(24.8)*
1	111 *(39.4)*
2	41 *(14.5)*
3	9 *(3.2)*
4	1 *(O.3)*
Unknown	50 *(17.7)*
Molecular abnormalities - n (%)	
KRAS	162 *(57.4)*
EGFR	8 *(2.8)*
ALK	2 *(0.7)*
BRAF	6 *(2.1)*
HER2	2 *(0.7)*
NRAS	1 *(0.35)*
PIK3CA	1 *(0.35)*
STK11	1 *(0.35)*
METamp	3 *(1.1)*
ROS1	1 *(0.35)*
FGFR	1 *(0.35)*
TP53	1 *(0.35)*
Wild type	93 *(33)*

Type of *KRAS* mutation - n *(%)*	
G12A	15 *(9.3)*
G12C	69 *(42.6)*
G12D	25 *(15.4)*
G12R	3 *(1.8)*
G12S	4 *(2.5)*
G12V	24 *(14.8)*
G13C	11 *(6.8)*
G13D	3 *(1.8)*
G13R	1 *(0.6)*
G13V	1 *(0.6)*
Unknown	6 *(3.7)*
Line of ICI - n (%)	
Maintenance	5 *(1.8)*
First line	24 *(8.5)*
Second line	149 *(52.8)*
Third line	68 *(24.1)*
Fourth line	24 *(8.5)*
Fifth line	8 *(2.8)*
Sixth line	2 *(0.7)*
Seventh line	2 *(0.7)*
Number of lines of ICI - n *(%)*	
1	264 *(93.6)*
2	18 *(6.4)*
Type of ICI - n *(%)*	
anti-PD-1	252 *(89.4)*
anti-PD-L1	19 *(6.7)*
anti-CTLA4	4 *(1.4)*
anti-PD1 + anti-CTLA-4	2 *(0.7)*
anti-PD-L1 + anti-CTLA-4	4 *(1.4)*
Other association	1 *(0.35)*
Name of ICI - n *(%)*	
nivolumab	249 *(88.3)*
pembrolizumab	3 *(1.1)*
atezolizumab	8 *(2.8)*
avelumab	4 *(1.4)*
durvalumab	7 *(2.5)*
ipilimumab	1 *(0.4)*
tremelimumab	3 *(1.1)*
durvalumab + tremelimumab	4 *(1.4)*
nivolumab + ipilimumab	2 *(0.7)*
nivolumab + urelumab	1 *(0.4)*

Table 1: Baseline population characteristics and ICI received.

PS = Performance Status, ICI = Immune Checkpoint Inhibitors, KRAS = Kirsten Rat Sarcoma Virus, EGFR = Epidermal Growth Factor Receptor, ALK = Anaplastic Lymphoma Kinase, NRAS = Neuroblastoma Rat Sarcoma Virus, PIK3CA = Phosphoinositide-3-Kinase, Catalytic, Alpha Polypeptide, STK11 = Serine Threonine Kinase 11, FGFR = Fibroblast Growth Factor Receptor, TP53 = Tumor Protein 53, anti-PD1 = anti-Programmed death-1 antibody, anti-PD-L1 = anti-Programmed death ligand 1 antibody, anti-CTLA-4 = anti-cytotoxic T-lymphocyte-associated protein 4 antibody

	KRAS m NSCLC	Non-*KRAS* m NSCLC	OR or HR [95% CI]	p value	NSCLC with other mutation	OR or HR [95% CI]	p value	Wild type NSCLC	OR or HR [95% CI]	p value
ORR	18.7%	14.4%	OR = 1.37 [0.71-2.63]	0.348	7.7%	OR = 2.76 [0.62-12.35]	0.184	16.3 %	OR = 1.18 [0.6-2.34]	0.633
DCR	48.4%	49.2%	OR = 0.97 [0.6-1.57]	0.900	50%	OR = 0.94 [0.41-2.15]	0.879	48.9%	OR = 0.98 [0.58-1.64]	0.936
PFS (months)	3.09 [2.36-3.82]	2.66 [1.98-3.34]	HR = 0.93 [0.71-1.21]	0.584	2.66 [1.39-3.93]	HR = 1 [0.62-1.6]	1.000	2.66 [1.71-3.62]	HR = 0.91 [0.69-1.21]	0.519
OS (months)	14.29 [9.64-18.95]	11.14 [7.4-14.9]	HR = 0.93 [0.68-1.29]	0.682	13.04 [7.71-18.37]	HR = 1.14 [0.64-2]	0.660	10.97 [4.74-17.21]	HR = 0.89 [0.62-1.24]	0.465
PFS > 6 months	30.2%	25.8%	OR = 1.25 [0.73-2.11]	0.417	25.9%	OR = 1.24 [0.49-3.12]	0.649	25.8%	OR = 1.25 [0.7-2.21]	0.451
PFS > 12 months	12.3%	11.7%	OR = 1.07 [0.52-2.21]	0.863	14.8%	OR = 0.81 [0.25-2.58]	0.722	10.8%	OR = 1.17 [0.52-2.62]	0.704

Table 2: Comparison of ICI efficacy in KRAS mutant NSCLC and other types of NSCLC.

KRAS = Kirsten Rat Sarcoma Virus, NSCLC = Non-Small Cell Lung Cancer, OR = Odds Ratio, HR = Hazard Ratio, CI = Confidence Interval, ORR = Overall Response Rate, DCR = Disease Control Rate, PFS = Progression-Free Survival, OS = Overall Survival

	Type of *KRAS* mutation					p value
	G12A (n=15)	**G12C (n=69)**	**G12D (n=25)**	**G12V (n=24)**	**G13C (n=11)**	
ORR	13.30%	18.50%	20%	18.20%	18.20%	0.99
DCR	46.70%	46.20%	52%	40.90%	54.50%	0.93
PFS (month)	2.66	3.09	3.91	2.69	4.6	0.96
OS (month)	Not reached	11.34	9.76	8.9	18.99	0.59
PFS > 6 month	20%	33.30%	32%	25%	36.40%	0.83
PFS > 12 month	6.70%	10.10%	20%	16.70%	18.20%	0.58

Table 3: Comparison of ICI efficacy with respect to different *KRAS* mutation subtypes

KRAS = Kirsten Rat Sarcoma Virus, ORR = Overall Response Rate, DCR = Disease Control Rate, PFS = Progression-Free Survival, OS = Overall Survival

	All patients	*KRAS* mutation	Other mutations	Wild type	p value
Number of patients (n analyzed/n all (%))	128/282 (45.4)	85/162 (52.5)	7/27 (26)	36/93 (38.7)	
Mean PD-L1 tumor expression [95% CI]	19.95 [14,13-25,77]	22.13 [14.66-29.6]	17.83 [-5.37-28.23]	15.65 [6.11-26.83]	
PD-L1 > 1% : n (%)	58 (*45.3)*	42 (*49.5)*	2 (*28.6)*	14 (*38.9)*	0.420
PD-L1 > 50% : n (%)	25 (*19.5)*	18 (*21.2)*	1 (*14.3)*	6 (*16.7)*	0.859

	G12A	G12C	G12D	G12V	G13C	Valeur de p
Number of patients (n analyzed/n all (%))	7/15 (46.6)	41/69 (59.4)	12/25 (48)	12/24 (50)	5/11 (45.5)	
Mean PD-L1 tumor expression [95% CI]	23.43% [-6.91-36.91]	22.98% [3.97-20.76]	22.7% [5.18-76.49]	23.66% [9.34-54.33]	21.18% [-6.54-70.94]	
PD-L1 > 1% : n (%)	3 (42.9)	14 (34.1)	7 (58.3)	10 (83.3)	3 (60)	0.033
PD-L1 > 50% : n (%)	1 (14.3)	4 (9.8)	5 (41.7)	4 (33.3)	2 (40)	0.039

Table 4: Analysis of PD-L1 expression
Panel A: in different groups
Panel B: for different *KRAS* mutation subtypes

KRAS = Kirsten Rat Sarcoma Virus, PD-L1 = Programmed death ligand 1, CI = Confidence Interval.