

ORIGINAL RESEARCH

Clinical characteristic and survival outcomes of patients with advanced NSCLC according to *KRAS* mutational status in the French real-life ESME cohort

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Purpose: The *RAS/MEK* signaling pathway is essential in carcinogenesis and frequently altered in non-small-cell lung cancer (NSCLC), notably by *KRAS* mutations (*KRASm*) that affect 25%-30% of non-squamous NSCLC. This study aims to explore the impact of *KRASm* subtypes on disease phenotype and survival outcomes.

Patients and methods: We conducted a retrospective analysis of the French Epidemiological Strategy and Medical Economics database for advanced or metastatic lung cancer from 2011 to 2021. Patient demographics, histology, *KRASm* status, treatment strategies, and outcomes were assessed.

Results: Of 10 177 assessable patients for *KRAS* status, 17.6% had *KRAS p.G12C* mutation, 22.6% had *KRAS non-p.G12C* mutation, and 59.8% were *KRASwt*. *KRASm* patients were more often smokers (96.3%) compared with *KRASwt* (85.8%). A higher proportion of programmed death-ligand 1 $\geq 50\%$ was found for *KRASm* patients: 43.5% versus 38.0% ($P < 0.01$). *KRASm* correlated with poorer outcomes. First-line median progression-free survival was shorter in the *KRASm* than the *KRASwt* cohort: 4.0 months [95% confidence interval (CI) 3.7-4.3 months] versus 5.1 months (95% CI 4.8-5.3 months), $P < 0.001$. First-line overall survival was shorter for *KRASm* than *KRASwt* patients: 12.6 months (95% CI 11.6-13.6 months) versus 15.4 months (95% CI 14.6-16.2 months), $P = 0.012$. First-line chemoimmunotherapy offered better overall survival in *KRAS p.G12C* (48.8 months) compared with *KRAS non-p.G12C* (24.0 months) and *KRASwt* (22.5 months) patients. Second-line overall survival with immunotherapy was superior in the *KRAS p.G12C* subgroup: 12.6 months (95% CI 8.1-18.6 months) compared with 9.4 months (95% CI 8.0-11.4 months) for *KRAS non-p.G12C* and 9.6 months (8.4-11.0 months) for *KRASwt* patients.

Conclusion: We highlighted distinct clinical profiles and survival outcomes according to *KRASm* subtypes. Notably *KRAS p.G12C* mutations may provide increased sensitivity to immunotherapy, suggesting potential therapeutic implications for sequencing or combination of therapies. Further research on the impact of emerging *KRAS* specific inhibitors are warranted in real-world cohorts.

Key words: real life data, NSCLC, *KRAS* mutational status, immunotherapy, prognosis

INTRODUCTION

The treatment landscape for non-small-cell lung cancer (NSCLC) is rapidly evolving and, following the principles of precision medicine, is becoming increasingly biomarker driven with new targeted therapies used in concert with companion molecular diagnostics.¹ NSCLC is associated with several addictive oncogenic driver alterations, e.g.

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epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *ROS* proto-oncogene 1 (*ROS1*), *B-Raf* proto-oncogene (*BRAF*) and neurotrophic tyrosine receptor kinase (*NTRK*), which are relevant for selecting the most beneficial regimen.^{2,3} New NSCLC biomarkers continue to emerge, including rearranged during transfection (*RET*) fusion, hepatocyte growth factor receptor (*MET*) exon 14 (ex14) skipping mutations and *MET* amplification, receptor tyrosine kinase erbB-2 (*ERBB2/HER2*) mutation, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) exon 2 *p.G12C* mutation, neuregulin (*NRG1*) fusion, and *EGFR* exon 20 insertions. Additionally, programmed death-ligand 1 (PD-L1) and tumor mutational burden can predict a better response to immune checkpoint inhibitors in NSCLC.

The mitogen-activated protein kinases (*MAPK*) form a group of proteins involved mainly in cell division, but also in many cellular processes such as apoptosis, cell differentiation, in response to various external signals (growth factors, osmotic stress, cytokines, etc.), in particular via the activation of intracellular signaling pathways.⁴ The most important of these pathways is the *RAS/RAF/MEK/ERK* pathway. Its alteration, leading to permanent activation, is a key process in carcinogenesis and can be caused by different processes, including excessive external stimulation (pathological accumulation of growth factors) or activating mutations affecting the different proteins of this cascade.⁵ The development of specific inhibitors of the different actors involved in this signaling pathway allowed to break the differentiation process and the abnormal multiplication responsible for tumorigenesis.

Historically, the first molecules targeting the *RAS/RAF/MEK/ERK* pathway targeted proteins located downstream, with anti-*BRAF* or anti-*MEK* therapies, particularly in melanoma and digestive cancers. More recently, molecules targeting the *RAS/RAF/MEK/ERK* pathway have arrived, but more upstream, with the development of therapies targeting the mutated form of the *KRAS* protein in its G12C form. Approximately 25%-30% of non-squamous NSCLC harbor a *KRAS* mutation (*KRASm*) in Western countries. These mutations mainly affect codons 12, 13, and 61. *KRAS* mutation is assumed to be associated with a poor prognosis. *KRASm* have been shown to be associated with shorter disease-free survival and overall survival in resected NSCLC,⁶ especially in the case of G12C subtype mutation.⁷ For advanced disease, the presence of a *KRASm* seems to be related to a shorter overall survival for patients treated with platinum-based chemotherapy.⁸ Before the era of immunotherapy, the prognostic and predictive values of the *KRASm* seemed to disappear in second line among patients who then received docetaxel or erlotinib as standard second-line therapies.⁹ On the contrary, regarding immunotherapy, *KRASm* tumors seem to have an associated inflammatory phenotype that would increase the sensitivity to immunotherapy.¹⁰

Mutations of the *KRAS* gene are generally mutually exclusive from other oncogene additions such as *EGFR* mutations or *ALK* rearrangement that are eligible for targeted therapy.^{11,12} Targeting *KRASm* is therefore a major

therapeutic advance.¹³ So far, two molecules have been approved for the treatment of *KRAS p.G12C*-mutated NSCLC after failure of platinum-based chemotherapy and immunotherapy targeting programmed cell death protein 1 (PD-1)/PD-L1: sotorasib (AMG510)^{14,15} and adagrasib (MRTX849).¹⁶ Still, the magnitude of benefit has been questioned in the second-line setting.

This non-interventional, retrospective, comparative study was conducted to describe baseline characteristics, treatment strategies, and outcomes of patients with advanced NSCLC according to their *KRAS* status included in the Epidemiological Strategy and Medical Economics (ESME) data platform for Advanced and Metastatic Lung Cancer (AMLC), before *KRAS* inhibitor market authorization. Our data may be of significant relevance for the subsequent development and sequencing of *KRAS* inhibitors in the treatment strategy of patients.

METHODS

Study design

The ESME Lung Cancer (ESME LC) database (clinicaltrials.gov NCT03848052) is a centralized, deidentified structured database derived from electronic health records of consecutive adult patients treated for lung cancer at 1 of the 38 health facilities (17 private non-profit comprehensive cancer centers spread over 19 sites, 1 center affiliated to the Unicancer network, and 18 university or general hospitals) participating in the ESME LC program. Patient-, hospitalization-, and pharmacy-related data are collected, including patient demographic characteristics, pathology, treatment strategies, and outcomes.

Unicancer manages the ESME LC data platform in accordance with current best practice guidelines. This platform is supervised by an independent scientific committee, which approved the present work. In compliance with French regulations, the ESME Data Warehouse was authorized by the French data protection authority [initial authorization number DE-2017-397 and subsequent amendment dated 14 October 2019, in accordance with General Data Protection Regulation (GDPR)]. Data are updated on a yearly basis and run into a data management process aimed at ensuring the quality of the data analyzed. No formal dedicated informed consent is required, but all patients have approved the use of their data.

Patient population

In this study, patient selection focused on patients with histologically confirmed advanced NSCLC, diagnosed from 1 January 2011. Patients were either newly diagnosed or relapsed from early-stage disease. To ensure at least 6 months of follow-up for patient outcomes, data were extracted from the ESME LC database on the data cut-off of 2 October 2021.

To better assess the specific impact of *KRAS* status, we excluded patients who did not have molecular analysis. We also excluded from our cohort those who presented a

targetable alteration in one of the known oncogenic drivers (*EGFR*, *ALK*, *BRAF*, *MET*, *ROS1* or *HER2*).

Data collection

The following data were collected: clinical characteristics [gender, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), co-morbidities, other cancer history); smoking status; disease characteristics (date and stage of primary tumor diagnostic and time to relapse/advanced disease, histological subtype, location of metastases); *KRAS* mutational status and other mutations; treatment strategy (number of treatment lines, therapeutic agents, disease evolution over time from index date, patient status at the end of each line, i.e. deceased, alive without progression or alive with progression and treatments received).

Survival status was collected. A treatment line was defined as a given therapeutic strategy delivered for metastatic NSCLC, until progression. The start date of the first-line therapy was defined as the date of the first systemic treatment initiated after diagnosis. Disease progression was defined as the occurrence of a new metastatic site or progression of existing metastases, regional tumoral or lymph node progression, or discontinuation of systemic treatment due to progression or death from any cause.

Statistical analyses

Demographic analyses were carried out on the entire cohort. Treatment and survival outcomes were restricted to the subpopulation with lung cancer diagnosed from 1 January 2015.

Data were summarized by median and range for continuous variables and by frequency and percentage for categorical variables. The number of missing data were presented for each variable, but not considered for the percentage calculations. Comparisons between groups were carried out using the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Overall survival was defined as the time from advanced disease to the date of death from any cause or end of follow-up at the cut-off date. OS₁ was defined as the time from the start date of first (OS₁) and second (OS₂) line of therapy to the date of death from any cause or end of follow-up at the cut-off date. Progression-free survival (PFS) was defined as the time from the start date of first (PFS₁) and second (PFS₂) line to the date of disease progression, or death from any cause or end of follow-up at the cut-off date. For time to event endpoint (overall survival and PFS), the Kaplan–Meier method was used to estimate median survival and survival rates at different time points. The hazard ratio and associated 95% confidence interval (CI) were estimated using a Cox proportional-hazards model. Survival analyses were only carried out when the available target population included at least 30 patients. Statistical analyses were carried out using SAS version 9.4 or higher (SAS Institute, Inc., Cary, NC).

RESULTS

Study population

A total of 22 137 patients with advanced NSCLC diagnosed from 1 January 2011 were registered in this observational cohort (Figure 1). Data were extracted from the ESME LC data platform on 2 October 2021. Patients without molecular testing ($n = 9845$) or with other druggable oncogenic alteration ($n = 1620$) were excluded. Patients with multiple *KRAS*_m recorded were also excluded ($n = 495$). Three subgroups of patients with demographic data and treatment outcomes were described according to their *KRAS* mutational status if available before first-line therapy start: *KRAS* *p.G12C* for patients with *KRAS* G12C mutation subtype ($n = 1791$), *KRAS non-p.G12C* for patients with *KRAS* mutation other than G12C ($n = 2297$), and *KRAS*_{wt} for patient with *KRAS* wild-type (wt) tumor ($n = 6089$). Treatment strategies and outcomes were described for patients whose advanced disease was diagnosed from 2015.

Patients and disease characteristics

Baseline characteristics for each cohort are summarized in Table 1. According to *KRAS* status (mutant versus wt): 39.9% versus 35.1% were women ($P < 0.01$); 3.8% versus 14.2% were non-smokers ($P < 0.01$). ECOG-PS and stage at NSCLC diagnosis status were similar. *KRAS*_m patients had more contralateral lung metastases: 28.9% versus 25.4% ($P < 0.01$) and bone metastases: 41.6% versus 38.0% ($P < 0.01$); and less pleural metastases: 6.2% versus 8.1% ($P < 0.01$) and liver metastases: 13.6% versus 15.4% ($P = 0.01$) than *KRAS*_{wt} patients. There was no difference regarding the prevalence of brain, meninges, or adrenal metastases. The proportion of patients with PD-L1 tumor proportion score (TPS) $\geq 50\%$ was superior for *KRAS*_m than *KRAS*_{wt} patients: 43.5% versus 38.0% ($P < 0.01$).

Among *KRAS*_m patients, 291 (7.1%) were *KRAS*^{G12A}, 1791 (43.8%) were *KRAS p.G12C*; 538 (13.2%) were *KRAS*^{G12D}, 756 (18.5%) were *KRAS*^{G12V}, 192 (4.7%) were *KRAS*^{G13C}, 136 (3.3%) were *KRAS*^{G13D}, and 384 (9.4%) had another *KRAS* mutation subtype (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmooop.2024.103473>). According to *KRAS* mutant subtype (*KRAS p.G12C* versus *KRAS non-p.G12C*): 41.5% versus 38.7% were women ($P = 0.07$); 1.5% versus 5.5% were non-smokers ($P < 0.01$); ECOG PS and stage at NSCLC diagnosis status were similar. There was no difference in the location of metastatic sites between the two subgroups, except for the adrenal metastases, with a higher prevalence for *KRAS non-p.G12C* patients (24.7% versus 20.9%; $P < 0.01$). PD-L1 expression levels (i.e. $\geq 50\%$) were similar for *KRAS p.G12C* patients and *KRAS non-p.G12C* patients (44.6% versus 42.7%; $P = 0.20$).

Overall survival according to *KRAS* mutational status and treatment lines

We assessed the impact of *KRAS* status on overall survival from advanced disease in all 7010 patients included in the ESME database, including patients who received no

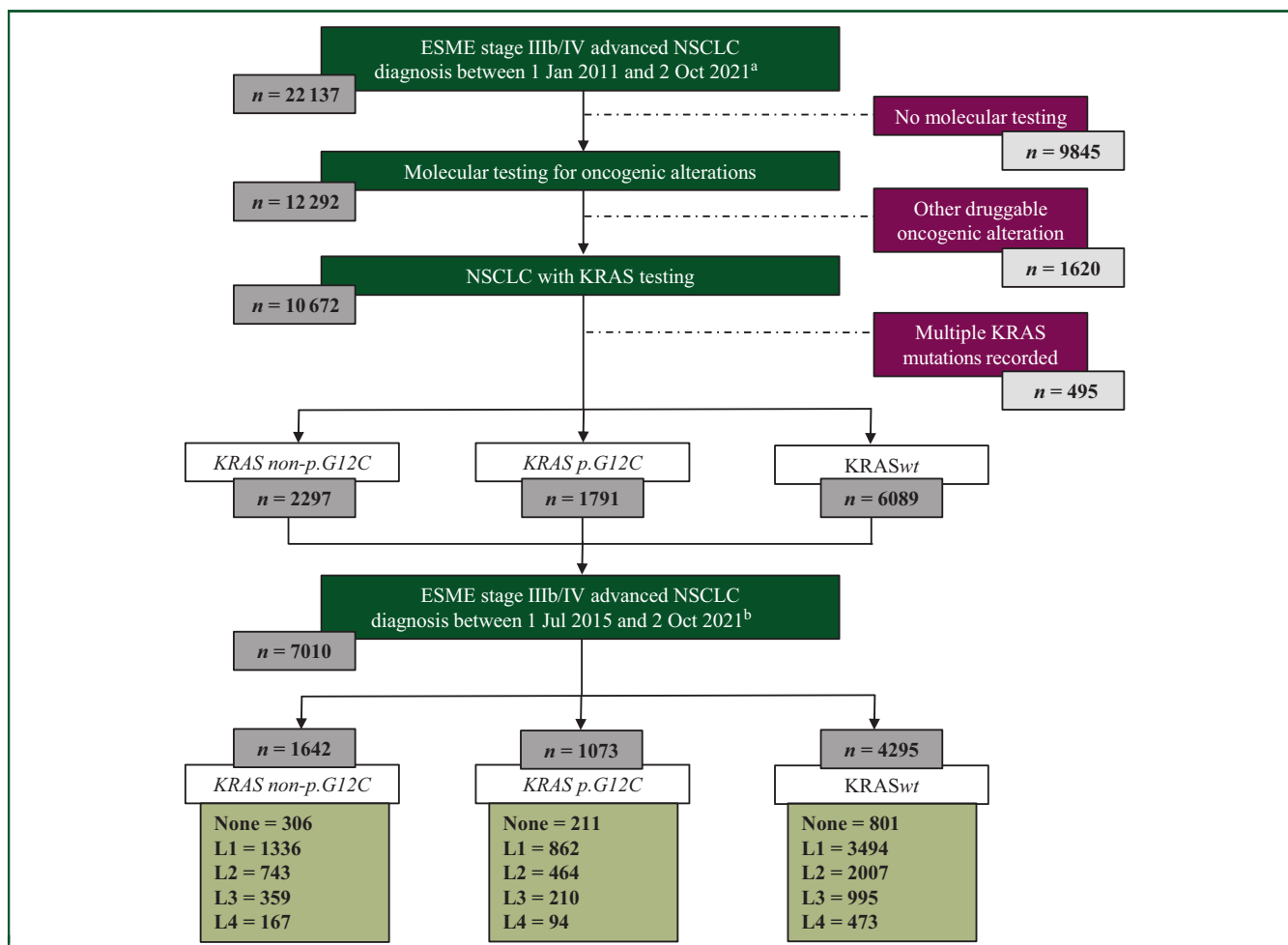


Figure 1. Flow chart.

ESME, Epidemiological Strategy and Medical Economics; NSCLC, non-small-cell lung cancer.

^aCohort used for demographic statistical analyses.

^bCohort used for analytic statistical analyses.

treatment (Figure 2). In this cohort, 306/1642 *KRAS non-p.G12C* patients (18.6%), 211/1073 *KRAS p.G12C* patients (19.7%), and 801/4295 *KRASwt* patients (18.6%) did not receive any treatment due to the aggressiveness of the disease. Patients with *KRASm* (G12C or non-G12C, $n = 2715$) had a non-significant lower overall survival than *KRASwt* patients ($n = 4295$): 13.0 months (95% CI 11.9-13.9 months) versus 15.0 months (95% CI 14.1-15.6 months), $P = 0.070$. According to *KRASm*, overall survival was similar for G12C mutations and non-G12C mutations: 12.2 months (95% CI 11.0 to 13.9 months) versus 13.4 months (95% CI 12.1 to 14.5 months), $P = 0.677$.

For patients who received at least one cancer treatment, *KRASm* were associated with worse survival. Median overall survival measured from the start of first-line treatment (OS1) was 12.6 months (95% CI 11.6-13.6 months) for *KRASm* patients versus 15.4 months (95% CI 14.6-16.2 months) for *KRASwt* patients ($P = 0.012$). Median OS1 according to *KRASm* subtype were as follows: 12.3 months (95% CI 10.9-14.7 months) and 12.7 months (95% CI 11.6-13.9 months) for *KRAS p.G12C* and *KRAS non-p.G12C*, respectively.

Among patients who were treated with two or more lines of treatment, the median overall survival from second-line

therapy (OS2) according to *KRASm* was as follows: 9.1 months (95% CI 7.2-10.9 months), 8.3 months (95% CI 7.4-9.4 months), and 10.3 months (95% CI 9.3-11.1 months) for *KRAS p.G12C*, *KRAS non-p.G12C*, and *KRASwt* subgroups, respectively. There was no significant difference of OS2 for *KRASm* versus *KRASwt* patients ($P = 0.064$).

Therapeutic strategies for front-line treatment and survival outcomes

At the time of patient recruitment, the main first-line strategy used for advanced disease was, in decreasing order of frequency: platinum-based chemotherapy without a PD-1/PD-L1 inhibitor (80%-83%), immunotherapy with anti-PD-1/PD-L1 as monotherapy (10%-13%), and chemotherapy associated with anti-PD-1/PD-L1 (6%-8%). For patients who received at least one therapy, overall survival from first-line start was longer for *KRASwt* ($n = 3494$) patients than for *KRASm* ($N = 2198$) patients ($P = 0.012$) (Figure 3).

In patients treated with chemoimmunotherapy in first line (L1), median OS1 was 48.8 months (95% CI 16.4 months to not reached) for the *KRAS p.G12C* cohort; 24.0 months (95% CI 15.5-37.1 months) for the *KRAS non-p.G12C* cohort, and

Table 1. Baseline patient and disease characteristics at advanced NSCLC.

	<i>KRAS</i> ^{wt} n = 6089	<i>KRAS</i> ^m n = 4088	P value	<i>KRAS</i> ^{G12A} n = 291	<i>KRAS</i> ^{G12C} n = 1791	<i>KRAS</i> ^{G12D} n = 538	<i>KRAS</i> ^{G12V} n = 756	<i>KRAS</i> ^{G13C} n = 192	<i>KRAS</i> ^{G13D} n = 136	<i>KRAS</i> ^{m^{other}} n = 384
Age			<0.01 ^a							
Median (years)	64.0	63.0		63.0	62.0	63.5	63.0	62.0	63.0	63.0
Gender			<0.01 ^b							
Female	2140 (35.1%)	1633 (39.9%)		106 (36.4%)	744 (41.5%)	224 (41.6%)	305 (40.3%)	61 (31.8%)	47 (34.6%)	146 (37.1%)
Smoking status			<0.01 ^b							
Non-smoker	831 (14.2%)	149 (3.8%)		13 (4.6%)	26 (1.5%)	44 (8.5%)	33 (4.6%)	3 (1.6%)	10 (7.5%)	20 (5.4%)
Smoker	5030 (85.8%)	3804 (96.2%)		269 (95.4%)	1709 (98.5%)	471 (91.5%)	692 (95.4%)	187 (98.4%)	123 (92.5%)	353 (94.6%)
Tobacco consumption			<0.01 ^a							
Median (pack-years)	34.0	40.0								
ECOG PS			0.70 ^b							
0-1	1044 (75.4%)	780 (74.6%)		55 (80.9%)	360 (74.4%)	105 (76.6%)	120 (75.0%)	39 (70.9%)	20 (64.5%)	81 (73.6%)
≥2	341 (24.6%)	265 (25.3%)		13 (19.1%)	124 (25.6%)	32 (23.4%)	40 (25.0%)	16 (29.1%)	11 (35.5%)	29 (26.4%)
Advanced disease modality			0.46 ^a							
De novo	5197 (85.4%)	3467 (84.8%)		255 (87.6%)	1517 (84.7%)	445 (79.7%)	638 (84.4%)	171 (89.1%)	113 (83.1%)	328 (85.4%)
Recurrent	892 (14.6%)	621 (15.2%)		36 (12.4%)	274 (15.3%)	93 (17.3%)	118 (15.6%)	21 (10.9%)	23 (16.9%)	56 (14.6%)
PD-L1			<0.01 ^b							
Negative	262 (12.7%)	186 (10.7%)		12 (9.6%)	70 (9.2%)	22 (10.0%)	40 (12.3%)	9 (12.5%)	6 (12.0%)	27 (14.3%)
1%-49%	1022 (49.4%)	799 (45.8%)		51 (40.8%)	353 (46.3%)	108 (49.3%)	143 (43.9%)	38 (52.8%)	24 (48.0%)	82 (43.4%)
≥50%	786 (38.0%)	759 (43.5%)		62 (49.6%)	340 (44.6%)	89 (40.6%)	143 (43.9%)	25 (34.7%)	20 (40.0%)	80 (42.3%)
Metastatic site										
Brain	1739 (30.9%)	1247 (32.6%)	0.11 ^b	83 (30.5%)	550 (32.7%)	164 (32.2%)	232 (32.9%)	63 (36.4%)	43 (32.5%)	112 (31.3%)
Leptomeningeal	39 (0.6%)	21 (0.4%)	0.39 ^b							
Liver	867 (15.4%)	520 (13.6%)	0.01 ^b	38 (14.0%)	216 (12.8%)	71 (13.9%)	96 (13.6%)	23 (13.3%)	21 (15.9%)	55 (15.4%)
Contralateral lung	1432 (25.4%)	1105 (28.9%)	<0.01 ^b							
Bones	2140 (38.0%)	1592 (41.6%)	<0.01 ^b	118 (43.4%)	678 (40.3%)	216 (42.4%)	288 (40.9%)	75 (43.4%)	52 (39.4%)	165 (46.1%)
Pleural effusion	457 (8.1%)	239 (6.2%)	<0.01 ^b							
Adrenal glands	1248 (22.2%)	883 (23.1%)	0.30 ^b							

ECOG PS, Eastern Cooperative Oncology performance status; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1.

^aKruskal-Wallis rank sum test.

^bPearson's chi-square test.

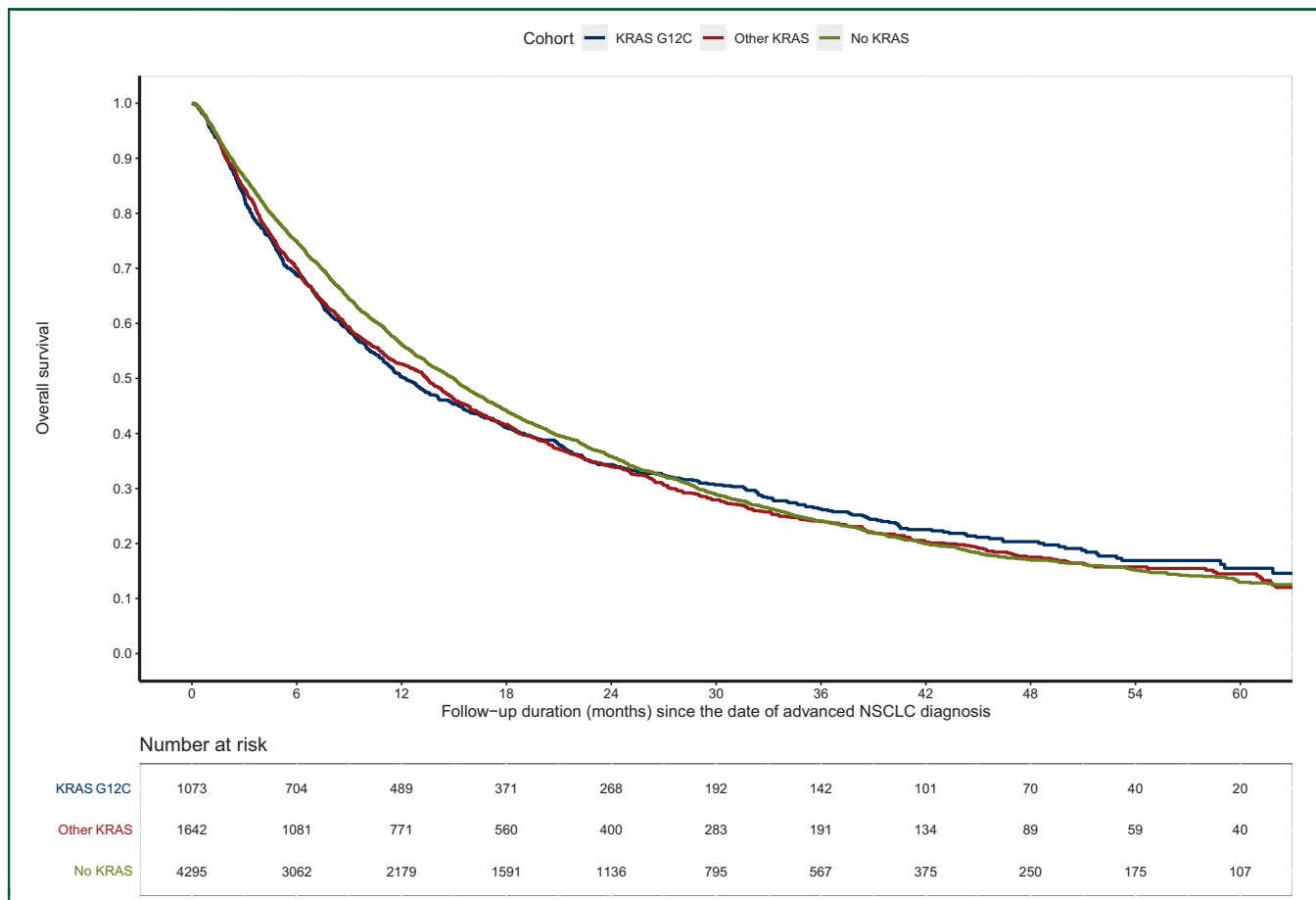


Figure 2. Overall survival according to KRAS mutation in patients included in the ESME AMLC database. NSCLC, non-small-cell lung cancer.

22.5 months (95% CI 18.9-28.4 months) for the *KRASwt* cohort. Regarding other therapeutic strategies, single-agent immunotherapy offered better overall survival than platinum-based chemotherapy, whether for *KRAS p.G12C* [20.2 months (95% CI 14.3-32.3 months) versus 11.0 months (95% CI 9.9-12.9 months)], *KRAS non-p.G12C* [15.9 months (95% CI 12.2-20.2 months) versus 11.6 months (95% CI 10.0-13.0 months)], and *KRASwt* [16.8 months (95% CI 13.0-21.3 months) versus 13.4 months (95% CI 12.4-14.2 months)] patients. Whatever the first-line strategy adopted, real-world progression-free survival (PFS1) was shorter in patients harboring *KRASm* (G12C or non-G12C) than in *KRASwt* patients: 4.0 months (95% CI 3.7-4.3 months) versus 5.1 months (95% CI 4.8-5.3 months), $P < 0.001$. Among *KRASm* patients, PFS1 was similar for *KRAS p.G12C* and *KRAS non-p.G12C* patients: 4.3 months (95% CI 3.8-4.7 months) versus 3.8 months (95% CI 3.5-4.2 months), $P = 0.268$.

Second-line treatment strategies and survival outcomes

A second line of treatment was administered in 43.2%, 45.2%, and 46.7% of patients in the *KRAS p.G12C*, *KRAS non-p.G12C*, and *KRASwt* subgroups, respectively (Figure 4). Main treatment strategies were as follows in decreasing order of frequency: PD-1/PD-L1 antibodies as monotherapy (58%-68%), platinum-based chemotherapy without a PD-1/PD-L1 drug

(19%-30%), docetaxel monotherapy, or combination (11%-13%). For patients who received at least two therapies, overall survival from second line (OS2) was longer for *KRAS p.G12C* patients than for *KRAS non-p.G12C* patients ($P = 0.003$).

The median overall survival from second-line initiation (OS2) of patients treated with immunotherapy was superior in the *KRAS p.G12C* subgroup: 12.6 months (95% CI 8.1-18.6 months) compared with the other groups: OS2 was 9.4 months (95% CI 8.0-11.4 months) for *KRAS non-p.G12C* and 9.6 months (8.4-11.0 months) for *KRASwt* patients. For *KRAS p.G12C* patients, median OS2 was higher with immunotherapy than with platinum-based chemotherapy [9.5 months (95% CI 6.1-13.4 months)] and docetaxel monotherapy or combination [6.6 months (95% CI 3.9-10.0 months)]. Similarly, for *KRAS non-p.G12C* patients, OS2 seemed higher with immunotherapy than with platinum-based chemotherapy [8.0 months (95% CI 5.7-12.7 months)] and docetaxel monotherapy or combination [6.1 months (95% CI 4.3-8.0 months)]. For *KRASwt* patients, OS2 was higher with platinum-based chemotherapy without a PD-1/PD-L1 drug [10.6 months (95% CI 8.9-12.1 months)] than with immunotherapy [9.6 months (95% CI 8.4-11.0 months)] or docetaxel monotherapy or combination [5.7 months (95% CI 4.3-7.7 months)].

Second-line median progression-free survival (PFS2) was 2.3 months (95% CI 2.0-2.8 months), 1.9 months (95% CI

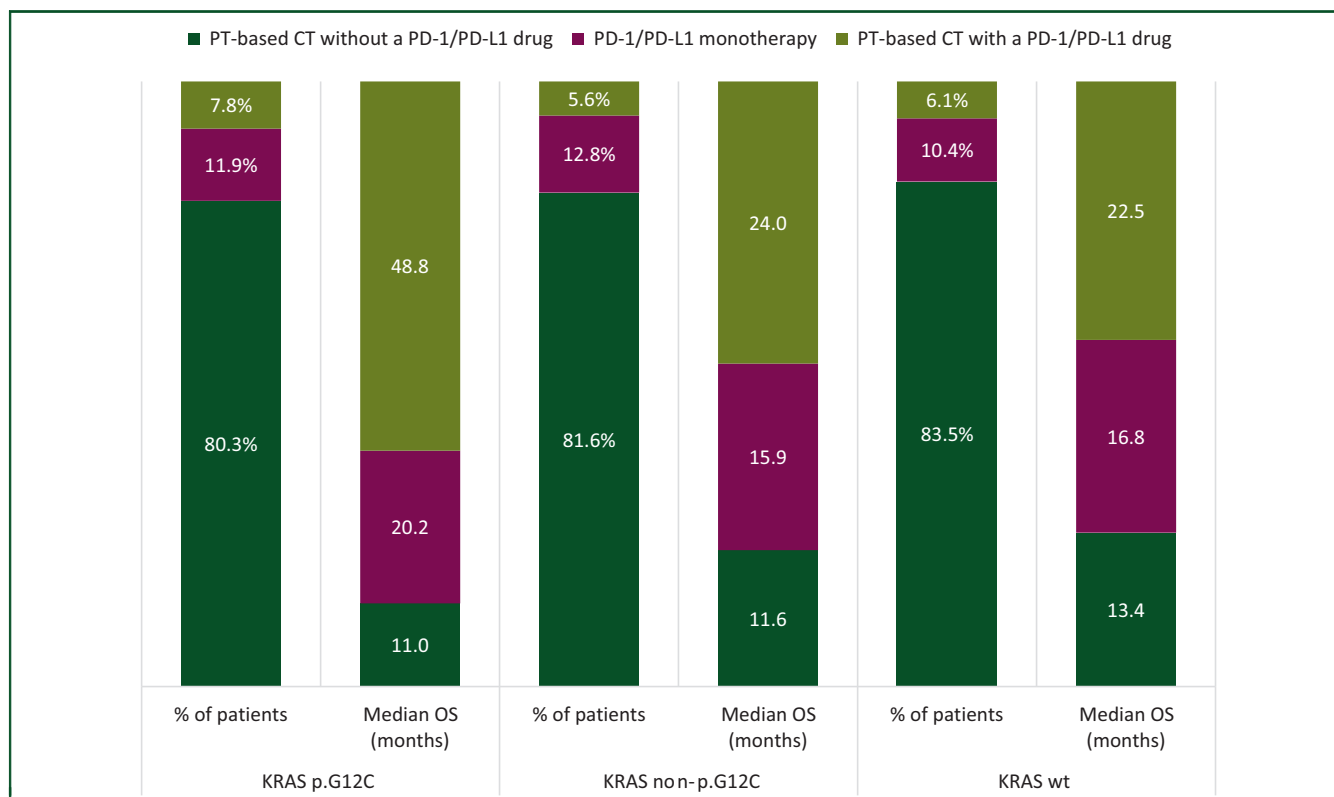


Figure 3. First-line treatment strategies and overall survival according to KRAS mutation subtype.

CT, chemotherapy; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PT, platinum.

1.7-2.2 months), and 2.8 months (95% CI 2.5-3.0 months) in the *KRAS p.G12C*, *KRAS^{non-G12C}*, and *KRASwt* subgroups, respectively. Overall, there were no significant PFS differences between *KRASm* and *KRASwt* patients ($P = 0.163$). According to *KRASm* subtypes, PFS2 was significantly higher for *KRAS p.G12C* than for *KRAS non-p.G12C* ($P = 0.004$). PFS2 was significantly higher in *KRASwt* patients than in *KRAS^{non-G12C}* patients ($P = 0.004$).

Metastatic localization evolution across treatment lines

We focused on the three most frequent metastatic sites from primary NSCLC outside of the lung: brain, bone, and liver. Across treatment lines, the percentage of patients with brain, liver or bone metastasis increased regardless of *KRAS* mutation status, i.e. with disease natural history (Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmoop.2024.103473>). *KRASm* patients (G12C or non-G12C) had slightly more brain and bone metastases than did *KRASwt* patients.

The prevalence of brain metastases was approximately one-third before first-line treatment: 31.2%, 30.7%, and 28.7% for patients in the *KRAS p.G12C*, *KRAS non-p.G12C*, and *KRASwt* subgroups, respectively. Brain metastases were symptomatic in 45.4%, 45.7%, and 44.6% of the patients. Despite the presence of brain metastases, overall survival from L1 was not modified across subgroups. OS1 was 12.9 months (with brain metastases) and 11.4 months (without brain metastases) for *KRAS p.G12C* patients. OS1 was 13.8 and 14.2 months for *KRAS non-p.G12C* patients. OS1 was

15.9 and 16.9 months for *KRASwt* patients. Similar results were observed for PFS1 according to the presence of brain metastases: PFS1 was 4.2 and 3.7 months in *KRAS p.G12C* patients with and without brain metastases; 3.1 and 4.0 months in *KRAS non-p.G12C* patients; and 4.6 and 5.1 months in *KRASwt* patients.

DISCUSSION

To our knowledge, this observational cohort is one of the largest published focusing on the impact of *KRAS* mutational status of patients with advanced NSCLC.¹⁷⁻²⁰ It offers a unique and detailed perspective on this population of interest as the targeting of *KRAS* mutations finally enters clinical routine with the market authorization of sotorasib and adagrasib.

This database is the result of a strong national initiative leading to the production of exhaustive real-life data concerning cancer patients treated in the main French cancer centers and therefore getting closer to real life. Among the 22 137 patients diagnosed with advanced NSCLC and consecutively included in this database during a 10-year period, *KRAS* status was evaluable for 10 177 patients. Of these, 1791 patients (17.6%) had a *KRAS p.G12C* mutation, 2297 (22.6%) had a *KRAS non-p.G12C* mutation, and 6089 (59.8%) had no *KRASm*. The G12C subtype corresponds to 43.8% of all the *KRASm* observed. These data are similar to those previously reported.²¹ Other druggable alterations were excluded from our cohort.

We decided to describe our cohort of patients according to their *KRAS* mutational status in three subgroups (*KRAS*

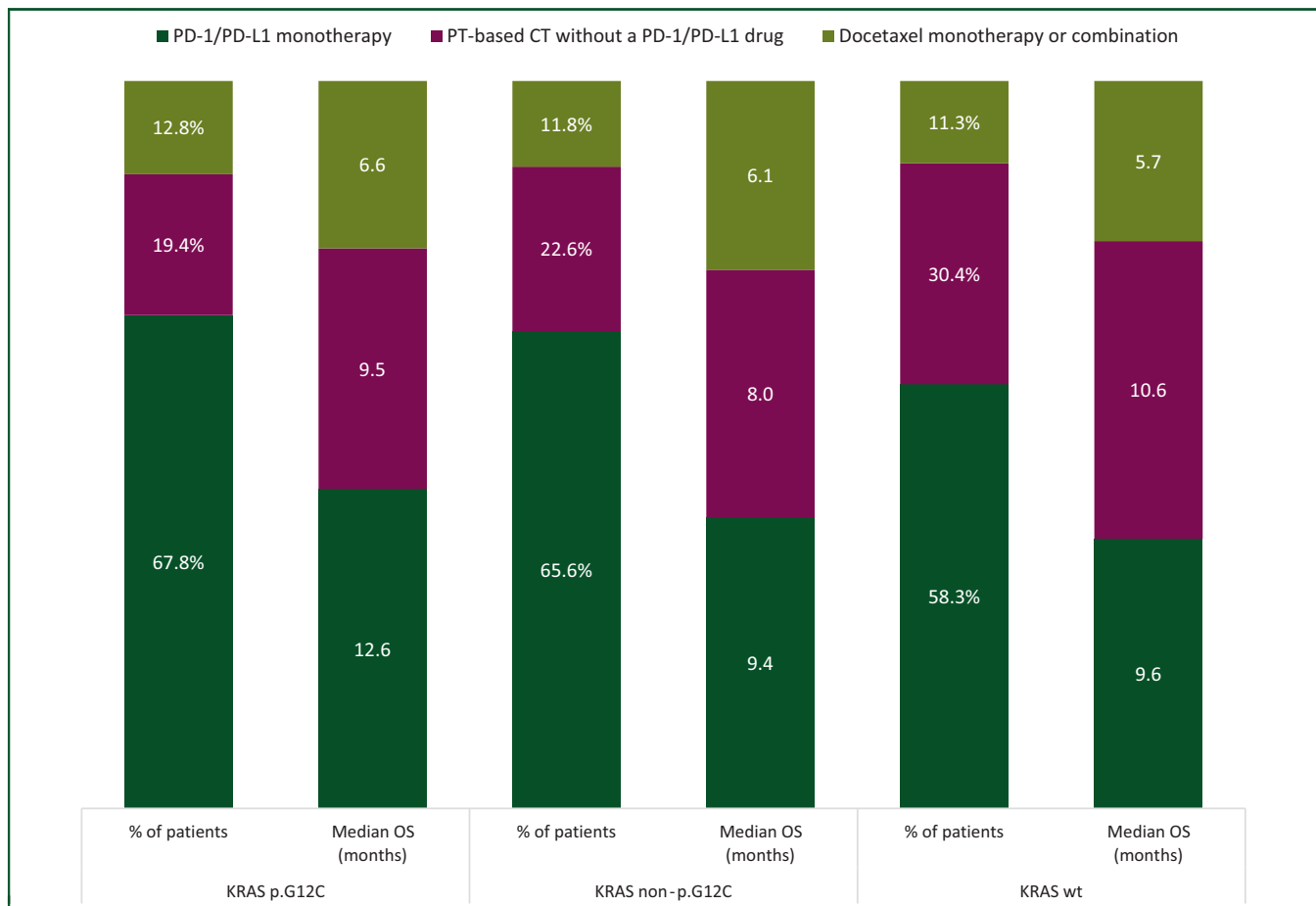


Figure 4. Second-line treatment strategies and overall survival according to KRAS mutation subtype.

CT, chemotherapy; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PT, platinum.

p.G12C versus *KRAS non-p.G12C* versus *KRASwt*) to evaluate its predictive and prognostic value on patient and disease characteristics and treatment outcomes. Gender and age were similar in the three subgroups. The prevalence of smoking (former or current smoker) was major in patients with *KRASm* (96.3%), notably *G12C* (98.5% and 94.5% for *KRAS p.G12C* and *KRAS non-p.G12C* patients, respectively) but it remains very frequent in *KRASwt* patients (85.8%).

The use and analysis of real-life data can naturally be criticized. The prospective nature of the recruitment of patients in our cohort, however, is a strong point. The study of PFS and overall survival of patients in this cohort reinforces the use of real-life data as a research basis or even as a comparative arm, as our data are similar to those published in randomized trials.²²⁻²⁵ At the beginning of this project, the combination of chemotherapy plus immunotherapy for first-line treatment in advanced NSCLC was not yet a therapeutic standard. In the *KRASwt* cohort, overall survival was similar to those reported in the KEYNOTE 189 study.²⁶ Regardless of *KRAS* status, immunotherapy used as monotherapy in first line provided a benefit in overall survival compared with chemotherapy as in the KEYNOTE 024 (pembrolizumab) and Impower 110 (atezolizumab) studies,^{27,28} and unlike CheckMate 026 (nivolumab).²⁹

Of greater importance, we show that *KRASm* NSCLC is associated with high expression of PD-L1 ($P < 0.01$). This observation may explain the excellent overall survival results observed in *KRASm* patients in our cohort treated by immunotherapy either alone or in combination with chemotherapy in a first-line setting. These results must be interpreted with caution, however, given the small numbers of patients receiving immunotherapy in first-line metastatic treatment line in our cohort due to the inclusion period of our study. As a second line of treatment, most patients received immunotherapy as monotherapy (58%-68%), platinum-based chemotherapy (19%-30%) or docetaxel used alone or in combination (11%-13%). We noticed a significantly higher overall survival in *KRAS p.G12C* patients (12.6 months) treated with immunotherapy compared with *KRAS non-p.G12C* (9.4 months) and *KRASwt* (9.6 months) patients. The benefit of immunotherapy compared with docetaxel independently of PD-L1 expression in terms of overall survival is consistent with that already shown in the CheckMate 057 and OAK studies.^{25,30}

In the next years, the impact on survival outcomes of the use of *KRAS p.G12C* specific inhibitors, such as sotorasib or adagrasib, will also need to be assessed in large real-life cohorts.³¹

Ultimately, our data provide some rationale for the subsequent development of *KRAS* inhibitors in metastatic *KRAS*^{mut} NSCLC, in the setting of immunotherapy-based therapies; this may include combination with immunotherapy alone, in PD-L1 $\geq 50\%$, or with chemo-immunotherapy whatever the PD-L1 status is, the latter strategy being more intensive in line with the aggressiveness of the disease. These combinations may be limited, however, due to the toxicity of the combination of *KRAS* inhibitors and immune checkpoint inhibitors, particularly liver toxicity for sotorasib. This may also be used in early-stage NSCLC as a neoadjuvant approach. Meanwhile, sequencing strategies may be assessed, with *KRAS* inhibitors used as maintenance, or even consolidation or adjuvant setting in non-metastatic NSCLC.

Conclusion

This study confirms the major impact of the presence of the *KRAS* mutation in NSCLC for both prognostic and predictive purposes. Notably, we highlighted the over-representation of former or current smoker patients in this population, which presented more aggressive forms of NSCLC compared with *KRAS*^{wt} patients (more stage IV at diagnosis, shorter PFS1 and OS1, regardless of the type of treatment). In addition, patients with *KRAS* *p.G12C*-mutated NSCLC have an increased sensitivity to immunotherapy in comparison with *KRAS non-p.G12C* mutations and *KRAS*^{wt} patients.

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DATA SHARING

The datasets analyzed for the current study were extracted from ESME LC Data Platform. In accordance with ethical and legal requirements related to the ESME data warehouse, individual data from the ESME databases cannot be made available. For any specific demand, please contact the corresponding author. Each demand will be examined on a case-by-case basis by the scientific committee.

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