Characteristics and treatment sequences of patients with *KRAS* G12C, other *KRAS* and *KRAS*-wild-type advanced or metastatic (AM) Non-Small Cell Lung Cancer (NSCLC) in the French ESME cohort

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Background: *KRAS* G12C mutation is found in 14% of NSCLC. Patients with *KRAS* G12C AM NSCLC have not been well characterized in routine clinical setting.

Objectives: to describe patients with *KRAS* G12C AM NSCLC and compare them to patients with other *KRAS* and *KRAS*-wild-type AM NSCLC.

Methods: We performed a retrospective observational cohort study of AM NSCLC patients included in the Epidemio-Strategy and Medical Economics (ESME) Lung Cancer Database and diagnosed between 2015 and 2022. Patients tested for *KRAS* mutation during the disease were divided in 3 subgroups: *KRAS* G12C (positive *KRAS* G12C mutation), other *KRAS* (positive for *KRAS* mutation other than G12C) and *KRAS*- wild-type (negative for all *KRAS* mutations).

Results: Among the 11580 *KRAS*-tested patients with contributive results, 1928 (17%) carried G12C, 2448 (21%) carried other *KRAS* mutations and 5203 (40%) harbored *KRAS* wild-type NSCLC (2001 patients tested positive for *EGFR*, *ALK*, *ROS1* or *BRAF* were excluded from the latest subgroup). Among *KRAS* G12C patients, 59% were male, and the median age was 63 years. The majority (98.5%) had a smoking history, 67% had an ECOG PS of 0-1 and 71% had *de novo* stage IV. The most frequent metastatic sites involved were bone (41%), brain (33%) and contralateral lung (28%). *STK11* appears to be the most common co-mutation (60%) when tested. When PD-L1 status was screened (62%), one third had PD-L1≥50%, and one third had PD-L1<1%. In 2015, most patients received platinum-based chemotherapy (CT) alone (92%) in the first line of treatment (LoT); this proportion decreased to 28% in 2020/2021 given the benefit of immunotherapy (IO) combined to CT or as monotherapy. In LoT 2, IO treatments were evenly used with a peak in 2018 to 68%. In LoT 3, IO and other treatments were quite stable over time. The patient and disease characteristics were similar in other *KRAS* and *KRAS*-wild-type patients, except a higher proportion of non-smokers (11%) and a less frequent *STK11* mutation (46%) in *KRAS*-wild-type patients than in the 2 other groups. Treatments were similar in the 3 subgroups except peaks of IO observed in LoT 2 in 2017-2018 and in LoT 3 in 2018 for other *KRAS* patients.

Conclusions: This large-scale real-world study shows that patient and clinical characteristics and treatment sequences of patients with *KRAS* G12C AM NSCLC are similar to those of other *KRAS* mutations or *KRAS*-wild-type patients except for the prevalence of *STK11* co-mutation and the proportion of non-smokers. It should be emphasized that the large majority of patients were treated in first-line before chemo-immunotherapy was approved. The gradual shift to first-line immunotherapy is therefore ongoing. Our findings describe accurately the landscape before arrival of the KRAS targeted drugs.