KRAS G12C Mutant Non–Small Cell Lung Cancer Linked to Female Sex and High Risk of CNS Metastasis: Population-based Demographics and Survival Data From the National Swedish Lung Cancer Registry

Johan Isaksson,[1,2] Anders Berglund,[3] Karly Louie,[4,#] Linda Willén,[2,5] Arash Hamidian,[6] Anders Edsjö,[7,8] Fredrik Enlund,[9] Maria Planck,[10] Anders Vikström,[11] Mikael Johansson,[5] Andreas Hallqvist,[12] Gunnar Wagenius,[13] Johan Botling[1,14]

Abstract

In a nation-wide cohort of NSCLC patients, reflex tested for driver mutations by NGS, we present detailed results on demographics, clinical baseline characteristics and survival associated with KRAS mutation status. We demonstrate significant differences between patients with KRAS G12C and other KRAS mutations related to male-female sex distribution, metastatic patterns associated with CNS disease, and impact on overall survival.

Background: Real-world data on demographics related to KRAS mutation subtypes are crucial as targeted drugs against the p.G12C variant have been approved. **Method:** We identified 6183 NSCLC patients with reported NGS-based KRAS status in the Swedish national lung cancer registry between 2016 and 2019. Following exclusion of other targetable drivers, three cohorts were studied: KRAS-G12C (n = 848), KRAS-other (n = 1161), and driver negative KRAS-wild-type (wt) (n = 3349). **Results:** The prevalence of KRAS mutations and the p.G12C variant respectively was 38%/16% in adenocarcinoma, 28%/13% in NSCLC-NOS and 6%/2% in squamous cell carcinoma. Women were enriched in the KRAS-G12C (65%) and KRAS-other (59%) cohorts versus KRAS-wt (48%). A high proportion of KRAS-G12C patients in stage IV (28%) presented with CNS metastasis (vs. KRAS-other [19%] and KRAS-wt [18%]). No difference in survival between the mutation cohorts was seen in stage I-IIIA. In stage IV, median overall survival (mOS) from date of diagnosis was shorter for KRAS-G12C and KRAS-other (5.8 months/5.2 months) vs. KRAS wt (6.4 months). Women had better outcome in the stage IV cohorts, except in KRAS-G12C subgroup where mOS was similar between

[1]Department of Immunology Genetics and Pathology, Science for life laboratory, Uppsala University, Uppsala, Sweden
[2]Center for Research and Development, Uppsala University/Region Gävleborg, Uppsala, Sweden
[3]Epistat AB, Uppsala, Sweden
[4]Amgen Ltd, Uxbridge, United Kingdom
[5]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden
[6]Amgen Sweden AB, Solna, Sweden
[7]Department of Clinical Genetics, Pathology and Molecular Diagnostics, Region Skåne, Sweden
[8]Division of Pathology, Department of Clinical Sciences, Lund University, Lund, Sweden
[9]Diagnostic center, Region Kalmar County, Sweden
[10]Division of Oncology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[11]Department of Pulmonary Medicine, Linköping University Hospital, Linköping, Sweden
[12]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[13]Cancer Theme, Karolinska University Hospital, Stockholm, Sweden
[14]Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Submitted: Feb 21, 2023; Revised: May 8, 2023; Accepted: May 8, 2023; Epub: 11 May 2023

Address for correspondence: Johan Botling, MD, PhD, Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, 41345 Gothenburg, Sweden
E-mail contact: johan.botling@gu.se

[#] Affiliation at the time the research was conducted.

https://doi.org/10.1016/j.cllc.2023.05.002

men and women. Notably, CNS metastasis did not impact survival in stage IV KRAS-G12C, but was associated with poorer survival, as expected, in KRAS-other and KRAS-wt. **Conclusion:** The KRAS p.G12C variant is a prevalent targetable driver in Sweden and significantly associated with female sex and presence of CNS metastasis. We show novel survival effects linked to KRAS p.G12C mutations in these subgroups with implications for clinical practice.

Clinical Lung Cancer, Vol. 24, No. 6, 507–518 © 2023 The Authors. Published by Elsevier Inc.

Keywords: NSCLC, Real-world data, Prognostic, KRAS mutation, NGS

Introduction

The treatment landscape in non–small cell lung cancer (NSCLC) is rapidly evolving with increasing focus on biomarkers for treatment decisions for the individual patient. At advanced stages, instead of administering chemotherapy, current best practice includes use of immunotherapy, in the form of checkpoint inhibitors, with or without concurrent chemotherapy, as well as targeted therapies based on the presence of oncogenic driver mutations.[1] Current diagnostic guidelines include treatment-predictive molecular testing for several genetic oncogenic driver aberrations for targeted therapy, as well as PD-L1 immunohistochemistry for immunotherapy.[2]

The two largest histologic subgroups of NSCLC, adenocarcinoma and squamous cell carcinoma, are genetically different with regard to patterns of acquired oncogenic mutations. Notably, targetable driver mutations are far more common in adenocarcinoma.[3,4] Lung cancer is strongly linked to smoking and this association is stronger in squamous cell carcinoma than in adenocarcinoma.[5] This link is strengthened further by the high prevalence of smoking associated mutations in squamous cell carcinoma, ie, in the tumor suppressor genes *TP53 and KEAP1*.[4] In contrast, adenocarcinomas show a greater genetic heterogeneity related to ethnicity, gender and smoking status.[6,7]

The RAS superfamily of intracellular proteins mediate cellular signal transduction and in turn regulate proteins involved in cell growth, differentiation and survival. Activating mutations in RAS-proteins are common in many solid human cancers, particularly in adenocarcinoma of the lung where up to 40% of patients, depending on demographic factors, harbor *KRAS* driver mutations.[8-11]

KRAS mutations are strongly associated with tobacco smoking, especially with regard to the most common *KRAS* variant in NSCLC: *KRAS* p.G12C.[12,13] Furthermore, co-mutations are of particular interest in *KRAS*-mutated tumors as some common co-mutations are linked to prognosis, distinct immune response patterns and response to treatment.[14,15]

The first *KRAS* p.G12C targeted therapy has been approved for patients with disease progression after first line systemic treatment. Also, combination therapy strategies with other drugs are under investigation in clinical trials.[16,17] Given the high prevalence of *KRAS* G12C mutations, this development has the potential to transform daily clinical practice and might improve survival prospects for a substantial part of the NSCLC patient population.

Sweden has a tax-financed health care system providing a uniform system for lung cancer diagnostics and treatment across geographic areas, socio-economic strata, and age groups.[18] The Swedish National Lung Cancer Registry (NLCR) contains data on demographics and diagnostic procedures, and linkage to the Swedish Cause of Death Registry allows comprehensive analysis of survival. Thus, access to a national registry with near complete inclusion rate in a setting with public uniform health care allows for analysis of truly population-based data.

KRAS-mutated NSCLC represents a large and markedly heterogenous group of tumors. Given the variability in mutation prevalence in different patient populations linked to ethnicity and smoking patterns and lack of knowledge on the specific biological properties of different KRAS-mutation variants, real-life data based on large population-based NSCLC cohorts are highly warranted. To this end, we aimed to explore the demographics and clinical outcomes in patients with KRAS-mutated tumors, with a focus on the p.G12C variant, using a large nationwide cohort of NSCLC patients.

Material and Methods

Patient Cohort and the National Lung Cancer Registry

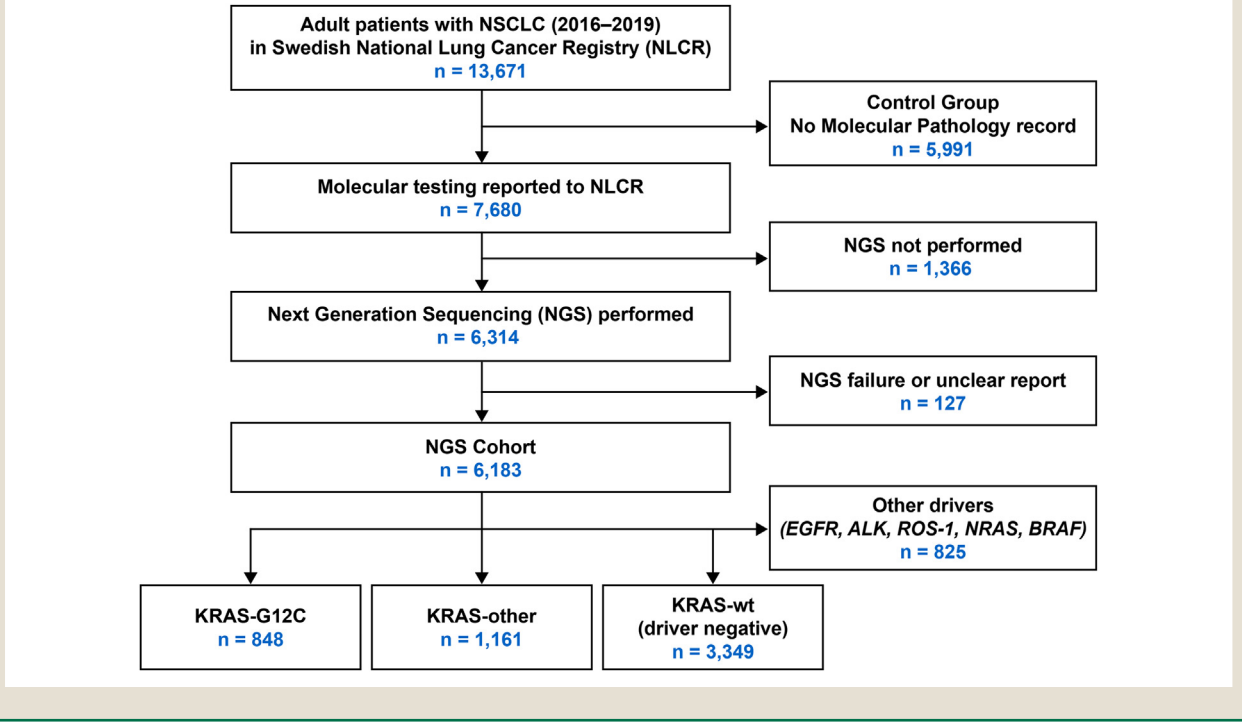
The study was performed according to the guidelines of the declaration of Helsinki. The study was approved by The Swedish Ethical Review Authority (reference 2021-03039).

The Swedish National Lung Cancer Registry includes information on diagnostic procedures and parameters such as date of diagnosis, histopathologic diagnosis, stage, location of primary tumor, performance status (PS) as well as metastatic pattern at diagnosis. The coverage of the registry is 97% of pathologically confirmed cases.[19] There has been a coordinated national implementation of tumor genetic testing for diagnostics, treatment, and follow-up of lung cancer patients in routine clinical practice, as targeted treatments have become available. Genetic testing is conducted on tissue biopsy and cytology samples at molecular pathology laboratories in Sweden. Between 2015 and 2018, reflex NGS panel analysis (including *KRAS* status) for all NSCLC was gradually introduced across the regions in Sweden using clinically validated commercial platforms or in-house designed panels with relevant coverage of aberrations in oncogenic driver genes (see below). Mutation status retrieved from the respective laboratory information systems have been reported to the NLCR molecular pathology module since 2015 at varying coverage levels between regional centers.

Data Extraction

A total of 13,671 unique patients with a NSCLC diagnosis between 2016 and 2019 were identified from the NLCR, and 7680 patients had a corresponding record in the molecular pathology

Figure 1 Patient source cohort in NLCR with data extraction of the NGS Cohort and sorting into mutational subgroups.



module (Figure 1). Data was extracted in August 2021. Patients without any molecular record (n = 5591) were included in the "Control Group." Patients with a molecular test other than NGS (n = 1366, ie, mainly PCR-based analyses of hot-spot mutations) or with NGS failure (n = 127) were excluded. The resulting NGS Cohort includes 6183 patients with conclusive NGS analysis. Following exclusion of patients with reported established driver aberrations (hotspot mutations in *EGFR, BRAF* or *NRAS*, and rearrangements in *ALK or ROS1*; n = 825), three cohorts were selected for further study: a cohort with no known driver mutation ("KRAS-wild-type [wt]"; n = 3349), a *KRAS* p.G12C cohort ("KRAS-G12C" n = 848) and a cohort with all other non-G12C *KRAS* mutation variants ("KRAS-other" n = 1161). For subgroup analysis based on histology, the cohorts were further divided into three groups, adenocarcinoma, squamous cell carcinoma, and NSCLC NOS (all other histologies, mainly adenosquamous carcinoma, and variants of large cell carcinoma). Demographic data for all cohorts and all histologic subtypes are shown in Table 1.

Statistics

Descriptive statistics for all subjects and analysis of associations between tumor mutation status and clinicopathological parameters were performed using Pearson's X^2 test or Fisher's exact test. Overall survival (OS) was defined from date of diagnosis to death of any causes, or end of study follow-up (June 30, 2021). The registry defines date of diagnosis as the date of the first histopathological or cytological test that confirms the NSCLC diagnosis. Survival analysis by Kaplan–Meier analysis was conducted for all subjects, by sex, stage at diagnosis, presence CNS metastasis, and within specific histological subgroups (adenocarcinoma, squamous cell carcinoma, and NSCLC NOS). In a subsequent step, mortality was evaluated in Cox regression models expressed as hazard ratios (HR) with 95% confidence intervals (CI) for individuals with adenocarcinoma and stage IV disease-for all subjects, and within the KRAS-G12C, KRAS-other, and KRAS-wt subgroups. All tests were two-sided, and a 5% level was considered statistically significant. Statistical analyses were performed using R version 4.1.2.

Results

NGS Cohort and Control Group

The NGS cohort, derived from the NLCR, represents 6183 NSCLC patients with reported conclusive molecular test results based on NGS (Table 1). In accordance with national guidelines, most patients in the Control Group were actually tested for driver mutations as well but lack a report of molecular status to the molecular pathology module in the registry. In addition, there are regional variations in testing practices regarding patients not eligible for systemic treatment (ie, low stage, poor PS) or in histologic subtypes where testing for driver mutations is not mandatory (ie, squamous cell carcinoma). To illustrate such bias, a comparison was made between the NGS Cohort and the Control Group.

Indeed, the prevalence of squamous cell carcinoma was higher in the Control Group compared to the NGS cohort (32.4% vs. 14.2%). Also, fewer patients in the Control Group presented with favorable PS 0 to 1 (60% vs. 68.3%) and more patients presented with PS 3 to 4 (16.6% vs. 11.4%). In the NGS Cohort, 54.3%

Table 1 Source Cohort of NSCLC Patients and the Mutational Subgroups

	KRAS-G12C	KRAS-Other	KRAS-wt	Other Drivers	NGS Cohort	Control Group
All subjects (%)	848 (100)	1161 (100)	3349 (100)	825 (100)	6183 (100)	5991 (100)
Female (%)	551 (65.0)	682 (58.7)	1590 (47.5)	536 (65.0)	3359 (54.3)	3017 (50.4)
Age at diagnosis, median [IQR]	71.0 [66.0, 75.0]	71.0 [66.0, 76.0]	72.0 [67.0, 77.0]	70.0 [63.0, 76.0]	72.0 [66.0, 77.0]	73.0 [67.0, 78.0]
Smoking status (%)						
Smoker	346 (40.9)	435 (37.5)	1240 (37.1)	138 (16.7)	2159 (35.0)	2228 (37.3)
Former smoker	480 (56.7)	641 (55.3)	1693 (50.6)	349 (42.4)	3163 (51.2)	3019 (50.6)
Never smoker	21 (2.5)	84 (7.2)	413 (12.3)	337 (40.9)	855 (13.8)	723 (12.1)
ECOG performance status (%)						
PS 0	233 (27.5)	332 (28.6)	922 (27.5)	302 (36.6)	1789 (28.9)	1696 (28.3)
PS 1	361 (42.6)	453 (39.0)	1311 (39.1)	310 (37.6)	2435 (39.4)	1898 (31.7)
PS 2	148 (17.5)	179 (15.4)	642 (19.2)	120 (14.5)	1089 (17.6)	1017 (17.0)
PS 3	62 (7.3)	126 (10.9)	311 (9.3)	67 (8.1)	566 (9.2)	748 (12.5)
PS 4	21 (2.5)	35 (3.0)	66 (2.0)	12 (1.5)	134 (2.2)	247 (4.1)
Missing	23 (2.7)	36 (3.1)	97 (2.9)	14 (1.7)	170 (2.7)	385 (6.4)
Stage at diagnosis (%)						
I	215 (25.4)	264 (22.7)	730 (21.8)	203 (24.6)	1412 (22.8)	1437 (24.0)
II	65 (7.7)	90 (7.8)	298 (8.9)	37 (4.5)	490 (7.9)	451 (7.5)
IIIA	69 (8.1)	101 (8.7)	380 (11.3)	48 (5.8)	598 (9.7)	563 (9.4)
IIIBC	64 (7.5)	84 (7.2)	364 (10.9)	55 (6.7)	567 (9.2)	551 (9.2)
IV	435 (51.3)	622 (53.6)	1577 (47.1)	482 (58.4)	3116 (50.4)	2989 (49.9)
Histology (%)						
Adenocarcinoma	759 (89.5)	1045 (90.0)	2177 (65.0)	789 (95.6)	4770 (77.1)	3365 (56.2)
Squamous cell carcinoma	18 (2.1)	34 (2.9)	808 (24.1)	15 (1.8)	875 (14.2)	1940 (32.4)
NSCLC NOS	71 (8.4)	82 (7.1)	364 (10.9)	21 (2.5)	538 (8.7)	686 (11.5)
Mutation prevalence (%)	**KRAS-G12C**	**KRAS-other**	**KRAS-wt**	**Other drivers**	**NGS Cohort**	
All subjects	848 (13.7)	1161 (18.8)	3349 (54.2)	825 (13.3)	6183 (100)	
Adenocarcinoma	759 (15.9)	1045 (21.9)	2177 (45.6)	789 (16.5)	4770 (100)	
Squamous cell carcinoma	18 (2.1)	34 (3.9)	808 (92.3)	15 (1.7)	875 (100)	
NSCLC NOS	71 (13.2)	82 (15.2)	364 (67.7)	21 (3.9)	538 (100)	

of patients were female compared to 50.4% in the Control Group. Smoking status, age and stage at diagnosis were largely similar. In summary, we consider the NGS Cohort representative for the general population of patients eligible for systemic treatment, with some expected bias resulting from different regional practices with regard to molecular testing of squamous cell carcinoma and testing strategies in patients with poor PS.

Demographics Linked to KRAS status

Patients in the NGS cohort were subdivided by mutational status into three molecular groups, KRAS-G12C, KRAS-other and KRAS-wt, and compared to each other (Table 1).

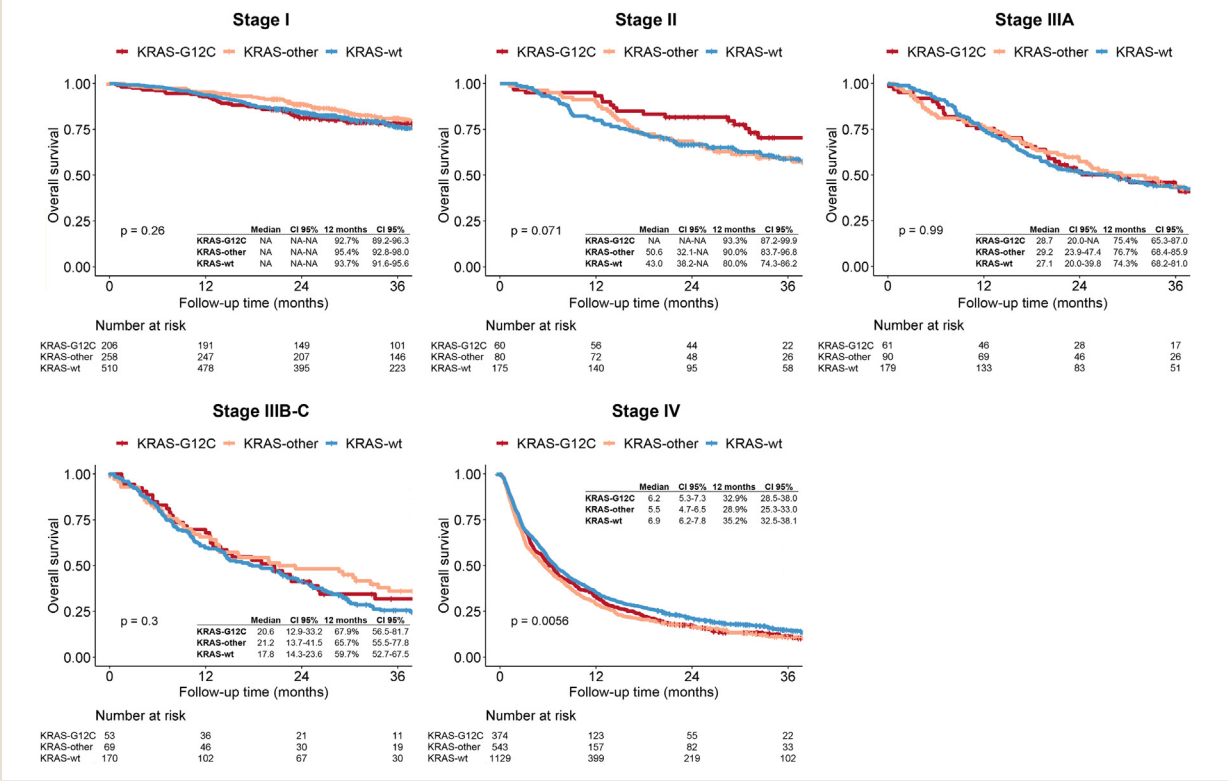
As expected, prevalence varied by histology with *KRAS* mutations being most common in adenocarcinoma. The prevalence of *KRAS* mutations were 32% in the overall NGS Cohort, 38% in adenocarcinoma, 28% in NSCLC NOS and 6% in squamous cell carcinoma. The fraction of *KRAS G12C* mutations amounted to 13.7% in the total NSCLC NGS cohort. The prevalence of *KRAS G12C* was 15.9% in adenocarcinoma, 13.2% in NSCLC NOS and 2.1% in squamous cell carcinoma, respectively. These results indicate that a significant number of *KRAS* mutations, including targetable *KRAS* G12C, will be missed unless NSCLC NOS and squamous cell carcinoma are routinely tested.

The fraction of female patients was high in the two KRAS groups, 65.0% in KRAS-G12C and 58.7% of KRAS-other, compared to 47.5% in KRAS-wt subgroup. Patients with a self-reported history of smoking were 86.2% in the total NGS cohort (35.0% current smokers and 51.2% former smokers) with similar numbers (87.7%) in the KRAS-wt group (37.1% current smokers and 50.6% former smokers). Higher numbers were found in the KRAS-G12C where reported incidence of smoking was 97.6% (40.9% current smokers and 56.7% former smokers). Advanced stage disease at time of diagnosis was largely similar between the mutation subgroups. Presentation in PS 0–1 was somewhat more common in KRAS-G12C (70.1%) compared to KRAS-other (67.6%) or KRAS wt (66.6%).

Survival Analysis By Stage

For survival analysis, we chose to focus on adenocarcinoma patients to avoid bias in regard to testing guidelines based on histologic subtypes. Also, the treatment options, based on national guidelines, for adenocarcinoma patients have been uniform across Sweden as opposed to more divergent practices for patients with

Figure 2 Kaplan-Meier curves for survival in adenocarcinoma by stage (I, II, IIIA, IIIB-C and IV) stratified by molecular subgroup.



squamous cell carcinoma. Figure 2 shows results from the Kaplan-Meier analysis of adenocarcinoma patients in stage I to IV comparing the KRAS-G12C, KRAS-other and KRAS-wt cohorts. The overall survival from date of diagnosis is based on all patients in the respective stage groups, across all PS strata and age groups, and includes treated and non-treated patients. Demographic data by stage can be found in Supplementary Tables 5A-E.

OS in stage I was similar between the mutation cohorts with 12-month survival above 90% in all groups. No statistically significant differences in survival could be detected. Median OS (mOS) was not reached in either group.

In stage II disease there was a trend towards improved survival in KRAS-G12C but it was not statistically significant ($P = .071$). In KRAS-G12C, mOS was not reached. In KRAS-other the mOS was 50.6 months and in KRAS-wt 43.0 months.

In stage IIIA no survival differences were detected between the three groups. The mOS ranged between 27.1 and 29.2 months. A similar pattern was seen in stage IIIBC with no difference in survival and mOS between 17.8 and 21.2 months.

In stage IV there was a small but statistically significant survival benefit for the KRAS-wt group ($P = .006$) at mOS of 6.9 months. The mOS for KRAS-G12C was 6.2 months and 5.5 months in KRAS-other.

Thus, in contrast to other published studies, we did not detect any significant survival differences linked to KRAS status in early-stage disease, nor in locally advanced disease.[20,21] There was a small but statistically significant difference in metastatic disease with poorer outcomes in *KRAS* mutated patients, but this was less pronounced in the KRAS-G12C group.

Men Versus Women

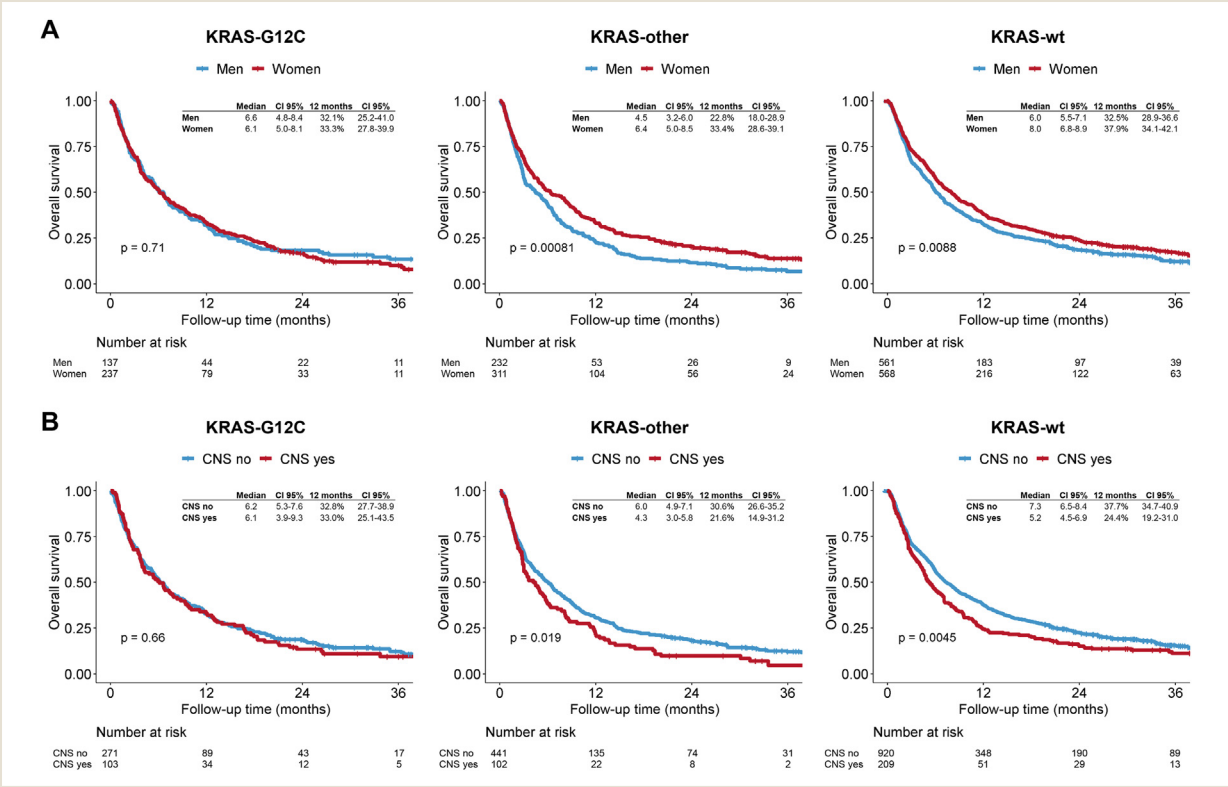
As the female-male ratios were different in the mutation subgroups, with a predominance of women in KRAS-G12C group, we next compared men and women in the adenocarcinoma subgroup. Demographic data is shown in Table 2 (data per stage is found in Supplementary Table 6A-E). Women with *KRAS* p.G12C were slightly younger than men (median 71 years vs. 72 years). Smoking history was almost identical. The fraction of patients with *KRAS* p.G12C in advanced stage at time of diagnosis was largely similar between the sexes, but PS was slightly more favorable in women (73.3% in ECOG PS 0–1, 69.4% in men). At stage 4 (Supplementary Table 6E), the metastatic pattern differed slightly between women and men; bone metastasis (38.0% vs. 43.1%) and adrenal gland metastasis (15.2% vs. 21.2%) were less common in women compared to men. Conversely, CNS metastasis were more common in women (28.7% vs. 25.5%).

Overall survival data from diagnosis in stage IV adenocarcinoma stratified by sex and *KRAS* mutation status is shown in Figure 3A. There was no statistical difference in mOS between women and men in the *KRAS* p.G12C cohort (6.1 months vs. 6.6 months). However, in the other two subgroups, survival differed in line with the established survival benefit linked to female sex. In the KRAS-

Table 2 Demographics of NGS Cohort Stratified by Sex (Adenocarcinoma)

	KRAS-G12C			KRAS-other			KRAS-wt		
	Male	**Female**	***P*-value**	**Male**	**Female**	***P*-value**	**Male**	**Female**	***P*-value**
All subjects	265	494		426	619		1055	1122	
Age at diagnosis, median [IQR]	72.0 [67.0, 76.0]	71.0 [65.3, 75.0]	.034	72.0 [67.0, 77.0]	71.0 [65.0, 75.0]	.002	72.0 [67.0, 77.0]	71.0 [65.0, 77.0]	.009
Smoking status (%)			.979			0.059			<0.001
Smoker	109 (41.1)	200 (40.6)		149 (35.1)	239 (38.6)		343 (32.6)	379 (33.8)	
Former smoker	149 (56.2)	279 (56.6)		252 (59.3)	327 (52.8)		587 (55.7)	519 (46.3)	
Never smoker	7 (2.6)	14 (2.8)		24 (5.6)	53 (8.6)		123 (11.7)	224 (20.0)	
ECOG performance status (%)			.090			.335			.441
PS 0	61 (23.0)	157 (31.8)		116 (27.2)	199 (32.1)		294 (27.9)	351 (31.3)	
PS 1	123 (46.4)	205 (41.5)		174 (40.8)	229 (37.0)		419 (39.7)	444 (39.6)	
PS 2	46 (17.4)	79 (16.0)		62 (14.6)	95 (15.3)		195 (18.5)	180 (16.0)	
PS 3	22 (8.3)	33 (6.7)		43 (10.1)	63 (10.2)		98 (9.3)	93 (8.3)	
PS 4	9 (3.4)	8 (1.6)		18 (4.2)	15 (2.4)		17 (1.6)	17 (1.5)	
Missing	4 (1.5)	12 (2.4)		13 (3.1)	18 (2.9)		32 (3.0)	37 (3.3)	
Stage at diagnosis (%)			.562			.681			.001
I	69 (26.0)	141 (28.5)		104 (24.4)	155 (25.0)		218 (20.7)	294 (26.2)	
II	19 (7.2)	41 (8.3)		29 (6.8)	53 (8.6)		106 (10.0)	69 (6.1)	
IIIA	25 (9.4)	37 (7.5)		34 (8.0)	56 (9.0)		87 (8.2)	94 (8.4)	
IIIBC	15 (5.7)	38 (7.7)		27 (6.3)	43 (6.9)		81 (7.7)	91 (8.1)	
IV	137 (51.7)	237 (48.0)		232 (54.5)	312 (50.4)		563 (53.4)	574 (51.2)	

Figure 3 Kaplan-Meier curves for survival in stage IV adenocarcinoma stratified by (A) sex and (B) presence of CNS-metastasis at diagnosis in the different molecular subgroups.



other cohort mOS for women was 6.4 months versus 4.5 months for men, and in KRAS wt mOS for women was 8.0 months versus 6.0 months for men. Although not statistically significant, the trend in multi-variable analysis supports a discordant survival impact related to female sex (Table 4) in the KRAS-G12C group after adjustment for age, PS and presence of CNS metastasis. The hazard ratios for death in women (vs. men as reference) were HR 1.21 in the KRAS-G12C group compared to HR 0.65 and HR 0.89 in KRAS-other and KRAS-wt groups, respectively. Thus, so far, we cannot explain this sex-related survival pattern by known baseline clinical confounders.

Metastatic Patterns

The metastatic patterns in stage IV adenocarcinoma were significantly different between the KRAS-G12C, KRAS-other and KRAS wt groups (Supplementary Table 5E). CNS metastasis was more common in KRAS-G12C (27.5%) compared to both KRAS-other (18.8%) and KRAS-wt (18.5%). Bone metastasis was more common in *KRAS*-mutated tumors, KRAS-G12C (39.8%) and KRAS-other (40.6%), compared to KRAS wt (35.0%). Similar patterns between the groups were seen in metastasis to the liver and adrenal glands. Metastasis to other sites, recorded as free text in the registry (not available for this study), were less common in KRAS-G12C (44.1%) compared to KRAS-other (55.1%) and KRAS-wt (50.3%).

CNS Metastasis and Concurrent Metastasis in Patients With KRAS p.G12C Mutations

As patients with CNS metastasis in stage IV adenocarcinoma were enriched in the KRAS-G12C subgroup, in comparison to KRAS-other and KRAS-wt, we next sought to study the mutation cohorts further with regard to the rate of metastasis at other anatomical sites in relation to reported presence of CNS metastasis at diagnosis (Table 3).

In the larger group of patients without CNS metastasis, bone metastasis was more common in patients with KRAS-mutations, ie, in the KRAS-G12C and KRAS-other subgroups, as described above. No significant differences between the mutation cohorts were detected for other metastatic sites. Notably, the metastatic rates at different sites were relatively similar between patients with *KRAS* p.G12C and other *KRAS* mutations.

In the group of patients with CNS metastasis, another pattern emerged. The rate of additional metastasis at other sites (bone, liver, adrenal gland, and other) was consistently lower for patients in the KRAS-G12C group in comparison to patients in the KRAS-other and KRAS-wt subgroups. This was especially striking for liver metastasis, 4.9% in KRAS-G12C versus 15.7% in KRAS-other and 14.8% in KRAS-wt. Also, the rate of concurrent metastasis in bone was lower in KRAS-G12C (19.4%) compared to KRAS-other (34.3%).

Table 3 KRAS Mutation Status and CNS Metastasis (Adenocarcinoma, Stage IV)

	With CNS Metastasis				Without CNS Metastasis			
	KRAS-G12C	KRAS-Other	KRAS-wt	*P*-value	KRAS-G12C	KRAS-Other	KRAS-wt	*P*-value
All subjects	103	102	210		271	442	927	
Female (%)	68 (66.0)	56 (54.9)	117 (55.7)	.168	169 (62.4)	256 (57.9)	457 (49.3)	<.001
Age at diagnosis, median [IQR]	70.0 [65.0, 74.0]	70.0 [64.0, 74.0]	70.0 [65.0, 75.0]	.623	71.0 [66.0, 76.0]	71.0 [65.3, 76.0]	72.0 [66.0, 77.0]	.268
Smoking status (%)				.062				<.001
Smoker	46 (44.7)	46 (45.1)	91 (43.3)		98 (36.3)	157 (35.6)	285 (30.8)	
Former smoker	56 (54.4)	49 (48.0)	98 (46.7)		161 (59.6)	251 (56.9)	466 (50.4)	
Never smoker	1 (1.0)	7 (6.9)	21 (10.0)		11 (4.1)	33 (7.5)	174 (18.8)	
ECOG performance status (%)				.277				.065
PS 0	9 (8.7)	14 (13.7)	32 (15.2)		42 (15.5)	63 (14.3)	156 (16.8)	
PS 1	43 (41.7)	41 (40.2)	79 (37.6)		115 (42.4)	161 (36.4)	347 (37.4)	
PS 2	30 (29.1)	17 (16.7)	54 (25.7)		60 (22.1)	94 (21.3)	211 (22.8)	
PS 3	12 (11.7)	20 (19.6)	30 (14.3)		30 (11.1)	75 (17.0)	138 (14.9)	
PS 4	6 (5.8)	3 (2.9)	6 (2.9)		11 (4.1)	27 (6.1)	24 (2.6)	
Missing	3 (2.9)	7 (6.9)	9 (4.3)		13 (4.8)	22 (5.0)	51 (5.5)	
Location of metastasis (%)								
Bone	20 (19.4)	35 (34.3)	47 (22.4)	.027	129 (47.6)	186 (42.1)	351 (37.9)	.012
Liver	5 (4.9)	16 (15.7)	31 (14.8)	.024	43 (15.9)	59 (13.3)	129 (13.9)	.628
Adrenal gland	14 (13.6)	21 (20.6)	36 (17.1)	.413	51 (18.8)	78 (17.6)	159 (17.2)	.816
Other	16 (15.5)	25 (24.5)	37 (17.6)	.213	149 (55.0)	275 (62.2)	535 (57.7)	.127
CNS only[a]	66 (64.1)	41 (40.2)	111 (52.9)	.003	-	-	-	-

[a] Subjects with bone, liver, adrenal gland, or other location of metastasis were excluded.

Table 4 Multivariable Analyses for Survival in Stage IV Adenocarcinoma (HR for Mortality)

			KRAS-G12C		KRAS-Other		KRAS-wt	
	HR	CI 95%	HR	CI 95%	HR	CI 95%	HR	CI 95%
KRAS mutation								
KRAS WT	1.00	reference	-	-	-	-	-	-
KRAS other	1.14	1.02-1.28	-	-	-	-	-	-
KRAS G12C	1.13	0.99-1.29	-	-	-	-	-	-
Age at diagnosis	1.01	1.01-1.02	1.02	1.01-1.04	0.99	0.98-1.01	1.02	1.01-1.02
Sex								
Male	1.00	reference	1.00	reference	1.00	reference	1.00	reference
Female	0.87	0.79-0.95	1.21	0.96-1.53	0.65	0.54-0.79	0.89	0.78-1.01
ECOG performance status (PS)								
PS 0-1	1.00	reference	1.00	reference	1.00	reference	1.00	reference
PS 2	2.11	1.87-2.37	1.84	1.40-2.42	2.16	1.71-2.74	2.20	1.88-2.56
PS 3+	6.03	5.29-6.88	6.14	4.44-8.49	5.98	4.72-7.57	6.44	5.36-7.76
Location of metastasis								
CNS no	1.00	reference	1.00	reference	1.00	reference	1.00	reference
CNS yes	1.20	1.07-1.35	1.08	0.84-1.39	1.19	0.94-1.51	1.28	1.09-1.52

We hypothesize that the common occurrence of CNS metastasis detected at diagnosis in *KRAS* p.G12C patients could reflect an early metastatic event linked to a higher probability of oligometastatic CNS disease in stage IV adenocarcinoma patients. Indeed, CNS metastasis reported as the sole metastatic event was more common in the KRAS-G12C subgroup (64.1%) in comparison to KRAS-other (40.2%) and KRAS-wt (52.9%).

CNS Metastasis and Survival

CNS-metastasis is a known negative factor for survival and morbidity in all solid tumors as well as in NSCLC. Figure 3B illustrates the survival outcome in the three mutation cohorts in relation to presence or absence of CNS metastasis. A significant difference in survival was seen in the KRAS-other subgroup - mOS with CNS metastasis 4.3 months and without 6.0 months. Similarly, in KRAS-wt the mOS was 5.2 months with CNS metastasis and 7.3 months without. In contrast, survival in the KRAS-G12C group was similar in the patients with or without CNS metastasis - the mOS with CNS metastasis was 6.1 months and without CNS metastasis 6.2 months.

In multi-variable analysis (Table 4), a significant negative survival impact was noted for presence of CNS metastasis in the total adenocarcinoma stage IV subgroup at HR 1.20 (CI 1.07-1.35). Likewise, an independent significant impact of CNS metastasis remained in the KRAS-wt cohort at HR 1.28 (CI 1.09-1.52). A similar trend, but non-significant was seen in the KRAS-other subgroup at HR 1.19 (CI 0.94-1.51). In concordance with the Kaplan-Meier analysis, the trend for survival impact related to CNS metastasis was less pronounced in the KRAS-G12C subgroup, at HR 1.08 (CI 0.84-1.39).

Thus, we were not able to find any obvious clinical baseline confounders that could explain the survival pattern associated with CNS metastasis in *KRAS* p.G12C mutated patients, except for the described pattern of concurrent metastasis at other anatomic sites.

Discussion

We here describe a population-based Swedish registry cohort of 6183 NSCLC patients with annotated driver mutations status based on NGS analysis in routine health care. To illustrate the impact of *KRAS* mutations on demographics, clinical baseline characteristics and overall survival, patient cohorts with *KRAS* p.G12C mutations, other *KRAS* mutations and a driver negative reference cohort were analyzed and compared.

KRAS mutation are common in NSCLC in western populations. Indeed, in the Swedish patient population the prevalence of *KRAS* mutations was high, 38% in adenocarcinoma and 28% in the NSCLC NOS cases. Similar frequencies have been reported for the non-squamous subgroups in other European populations.[9,10] The p.G12C variant was seen at 15.9% and 13.2% in adenocarcinoma and NOS patients, respectively. Thus, *KRAS* p.G12C mutations represent the most common targetable driver aberration in the Swedish lung cancer population.

Given the approval of specific therapeutic inhibitors, the presence of a significant number of p.G12C mutations in squamous cell carcinoma indicate that current guidelines for molecular testing need to be revised.[22] *KRAS* p.G12C mutations at 2.1% in squamous cell carcinoma represents a larger targetable fraction than aberrations such as *BRAF, ROS1, RET* or *MET* exon 14 skipping in the adenocarcinoma subgroup. Adding reported "other drivers" at 1.7% (Table 1) would indicate that 3.8% of the squamous cell carcinoma patients, if tested, could be candidates for targeted therapy. The presence of driver mutations in true squamous NSCLC has been questioned given the difficulty to assess histologic subtypes in small cytology and biopsy specimens. However, the registry data shows that Swedish pathologists, that applied the guideline algorithms from 2011, annotate a significant fraction of cases with driver mutations as squamous cell carcinomas. In addition, it should be noted that suggested "rescue" procedures to focus molecular testing on young patients and never smokers with squamous cell carcinoma

would not be effective for the *KRAS* p.G12C population, as shown here.

The survival outcome data in this study showed no significant impact of *KRAS* status in stage I to IIIB disease. This contrasts with a recent study by the ETOP group on surgical NSCLC cases where *KRAS* p.G12C cases exhibited worse survival outcome than cases with other *KRAS* mutations, and better survival was seen in *KRAS*-negative patients. However, in the ETOP study, the *KRAS* negative group also included other driver mutations,[20] in contrast to our study set-up.

In stage IV disease, KRAS-wt had a small but statistically significant better survival outcome. In comparison, other studies have failed to show significant differences in survival comparing *KRAS* mutant and non-mutated cases, or between patients with *KRAS* p.G12C and other *KRAS* mutations.[23–25] In the context of immunotherapy, some studies have shown more favorable outcomes in *KRAS*-mutated cases, while other studies have not.[26,27] Although low at 5.5 to 6.9 months, the mOS is comparable to historic data in a treatment environment with chemotherapy as the primary option,[28] as well as to real-world data, from the same time period as this study, where chemotherapy was the most common first line treatment.[29] The three mutation cohorts all had the same treatment options available for the duration of the study, primarily guided by ECOG PS. The survival analyses included all patients, including patients with poor ECOG PS which negatively affects the observed median overall survival. It is important to consider that a substantial number of patients likely received no treatment at all due to ECOG PS or by their own choice. Thus, our findings to a large extent reflect prognostic effects of the particular mutation subtypes rather than treatment-predictive impact.

Results on the sex distribution in *KRAS* mutated and *KRAS* p.G12C patients are conflicting. Other European studies show fairly equal distribution between men and women.[25,30] Notably, in our study, 65.0% of KRAS-G12C, and 58.7% of KRAS-other were women. This finding is in agreement with a US study (61.1% women in *KRAS* p.G12C group), findings in a retrospective Norwegian cohort (*KRAS* mutated, not separated for *KRAS* p.G12C with 56.9% women) and data from the Lung Cancer Consortium (57.9% women).[24,31,32] In contrast, a Chinese study has showed a large majority of men (85.2%) in the *KRAS* p.G12C patient group.[33] We believe that the sex distribution can be explained by differences in ethnicity as well as male and female smoking habits. In addition, a high rate of smoking related mutations (ie, *KRAS* p.G12C) have been described in women, at comparable or lower tobacco consumption.[34,35]

Treatment outcomes in NSCLC are generally better in women[36,37] regardless of stage and treatment modality, including immunotherapy.[38] Our finding that men and women in the KRAS-G12C subgroup have the same survival outcome in stage IV adenocarcinoma is intriguing. We can only speculate on the causes underpinning this result. We could not find any obvious confounding registry parameter that could explain the lack of survival impact related to female sex in the KRAS-G12C group. Further studies on the distribution of prognostic co-mutations and treatment response after chemotherapy and immunotherapy in men versus women are warranted to better understand this finding.[14,39,40]

KRAS mutations have been shown to be linked to an increased risk of brain metastases in other solid tumors.[41,42] Our study shows a high prevalence of CNS metastasis at diagnosis in the stage IV KRAS-G12C group (26.7%). This fraction is slightly larger than in the study by Spira et al.[31] which describe CNS metastases in 23.4% of patients with *KRAS* p.G12C mutations. Notably, in our cohort, the frequencies of CNS metastases were similar in the KRAS-other and KRAS-wt groups (19.1% and 18.5%). This result indicates that the enrichment of CNS metastasis linked to *KRAS* mutations in NSCLC is driven mainly by the p.G12C mutation. In general terms, the results related to *KRAS* mutations mirror findings in other oncogenic driver subsets of NSCLC that also present with a high rate of CNS metastasis.[43]

Brain metastases are one of the leading causes of morbidity and mortality in NSCLC.[44] Under current Swedish and European guidelines,[45] patients with confirmed metastatic disease on CT scans of thorax/abdomen are not required to undergo CT/MRT of the brain. Thus, asymptomatic brain metastases are likely underreported in our registry study. Still, the high fraction of reported CNS metastasis raise the question whether *KRAS* p.G12C mutated patients should be screened for CNS metastasis during the diagnostic work-up. Targeted therapies directed at other driver mutations have been shown to be superior compared to chemotherapy, and current treatment standards recommend initial treatment with tyrosine kinase inhibitors and evaluation rather than radiotherapy in *EGFR/ALK* positive NSCLC with brain metastases.[46–48] New targeted therapies against *KRAS* p.G12C might be an additional first-line treatment modality for this patient category.

Interestingly, we could not demonstrate any impact on mOS related to the presence of CNS metastasis in KRAS-G12C group of stage IV adenocarcinoma. Given the known link between CNS metastasis and poor outcome, worse survival was expected. Indeed, a negative survival impact of CNS metastasis was seen in the KRAS-other and KRAS-wt groups. We can only speculate on the mechanisms behind this finding. One possible explanation is that *KRAS* mutated patients with brain metastasis, as described, responds well to immunotherapy.[49,50] Another possible explanation is that intrinsic biological properties of *KRAS* p.G12C mutations are linked, not only to a high frequency of CNS metastasis, but also to early metastatic dissemination to the CNS. This hypothesis is supported by a higher proportion of patients presenting with CNS metastasis as the only metastatic site. If confirmed in other studies, patients with the combination of a CNS metastasis and *KRAS* p.G12C could represent a specific oligometastatic subgroup in lung adenocarcinoma with a comparatively favorable survival outcome.

The strengths of this study lie in the size and the high degree of patient coverage in a population with equal access to health care and advanced diagnostics rather than being based on cohorts from clinical studies or selected specialist centers. The main weakness, as discussed, is the lack of follow-up data after systemic treatments, in relation to the survival results in stage IV adenocarcinoma subgroups. Ongoing retrospective registration of treatment and follow-up data in the NLCR will allow future detailed studies on the predictive impact of KRAS mutation subtypes in relation to chemotherapy and checkpoint inhibitor regimens. Also, as co-mutations beyond driver mutations such as *TP53, KEAP1* and

STK11 were not reported to the registry, we were not able to assess the impact of these in the respective mutation sub-cohorts.

In conclusion, real-world data from the national lung cancer registry indicate that *KRAS* p.G12C is the most common targetable aberration in the Swedish NSCLC population, and significantly linked to baseline parameters such as smoking, female sex, and presence of brain metastasis. We believe that the distribution of *KRAS* p.G12C across all histologic subtypes warrants molecular testing of all NSCLC patients. Reflex radiologic brain scans at diagnosis in patients with *KRAS* p.G12C mutations should be discussed based on the high frequency of CNS metastasis and hypothesis generating data indicating the brain as a vulnerable compartment for early metastatic dissemination.

Clinical Practice Points

This large, population-based, study illustrates key demographic findings related to the *KRAS* G12C mutation subtype. It is the most common targetable oncogenic driver in NSCLC in a typical western population, has a strong correlation to smoking and is predominantly seen in women.

- A significant prevalence of *KRAS* G12C in NSCLC-NOS (13.2%) and squamous cell carcinoma (2.1%) highlights the need for NGS testing in all histologic NSCLC subtypes, in addition to lung adenocarcinoma.
- The link between *KRAS* mutations and CNS metastasis is strongly attributed to the *KRAS* G12C variant. In addition, as opposed to patients with other KRAS mutations, the majority of stage IV patients with KRAS G12C presented with CNS metastasis as the sole metastatic compartment. Thus, we suggest that CT/MRI brain scans should be considered in KRAS G12C patients to discover isolated asymptomatic CNS disease for potential treatment.
- Lack of overall survival differences in stage IV disease between men and women, and between patients with and without CNS metastasis, are unique findings which warrant further research into the distinct biology of *KRAS* G12C mutated NSCLC.

Disclosure

The study was funded by Amgen Ltd

Johan Isaksson declares research grants from Amgen Sweden AB. Lecture honoraria from Amgen Sweden, AstraZeneca, BMS, MSD and Roche. Participation in advisory boards for Amgen, AstraZeneca and Roche

Anders Berglund declares no conflicts of interest outside funding of the study.

Karly Louie was an employee of Amgen Ltd while conducting the research and holds stock options in Amgen and Biomarine.

Linda Willén declares lecture honoraria and consulting fees from BMS

Arash Hamidian is an employee of Amgen Sweden and holds company stock.

Anders Edsjö declares lecture honoraria from Amgen, AstraZeneca, Bayer and Diaceutics

Fredrik Enlund declares lecture honoraria from AstraZeneca, BMS, Boehringer-Ingelheim, Novartis, PierreFabre and Pfizer.

Maria Planck declares research grants from the Swedish Cancer society, the Sjöberg foundation and the Kamprad foundation outside the scope of this study as well as lecture honoraria from Roche.

Anders Vikström declares research support from Boehringer-Ingelheim, lecture honoraria from Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, MSD, Novartis, Pfizer, Roche and Takeda. Travel support from Roche. Advisory board participation from AstraZeneca, Boehringer-Ingelheim, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and Takeda

Mikael Johansson declares no conflict of interest outside study funding

Andreas Hallqvist declares research grants from AstraZeneca and Novartis. Lecture honoraria from AstraZeneca, BMS and Roche.

Gunnar Wagenius declares no conflicts of interest outside funding of the study.

Johan Botling declares research grants from BMS, consulting fees and stock options from Strike Pharma and travel support from Amgen Sweden as well as lecture honoraria from Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, GSK, Illumina, Lilly, MSD, Novartis, Pfizer and Roche.

Acknowledgments

This study was sponsored by Amgen Ltd (Uxbridge, United Kingdom). The authors gratefully acknowledge support and scientific input from the National Lung Cancer Registry (NLCR), the Swedish Lung Cancer Study Group (SLUSG), and the Solid Tumor working group in the Genomic Medicine Sweden initiative. The authors thank clinicians, pathologists and staff at the Swedish lung cancer care units and molecular pathology laboratories for reporting clinical and molecular data to the NLCR.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2023.05.002.

References

1. Hanna NH, Schneider BJ, Temin S, et al. Therapy for stage IV non-small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol*. 2020;38(14):1608–1632. doi:10.1200/jco.19.03022.
2. Hanna NH, Robinson AG, Temin S, et al. Therapy for Stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol*. 2021;39(9):1040–1091. doi:10.1200/jco.20.03570.
3. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543–550. doi:10.1038/nature13385.
4. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489(7417):519–525. doi:10.1038/nature11404.
5. Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer*. 2012;12:385. doi:10.1186/1471-2407-12-385.
6. Forsythe ML, Alwithenani A, Bethune D, et al. Molecular profiling of non-small cell lung cancer. *PLOS ONE*. 2020;15(8). doi:10.1371/journal.pone.0236580.
7. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48):78985–78993. doi:10.18632/oncotarget.12587.
8. La Fleur L, Falk-Sörqvist E, Smeds P, et al. Mutation patterns in a population-based non-small cell lung cancer cohort and prognostic impact of concomitant mutations in KRAS and TP53 or STK11. *Lung Cancer*. 2019;130:50–58. doi:10.1016/j.lungcan.2019.01.003.
9. Boch C, Kollmeier J, Roth A, et al. The frequency of EGFR and KRAS mutations in non-small cell lung cancer (NSCLC): routine screening data for central Europe from a cohort study. *BMJ Open*. 2013;3. doi:10.1136/bmjopen-2013-002560.
10. Dearden S, Stevens J, Wu YL, et al. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol*. 2013;24(9):2371–2376. doi:10.1093/annonc/mdt205.

11. Judd J, Abdel Karim N, Khan H, et al. Characterization of KRAS mutation subtypes in non-small cell lung cancer. *Mole Cancer Ther*. 2021;20(12):2577–2584. doi:10.1158/1535-7163.Mct-21-0201.
12. Thunnissen FB, Prinsen C, Hol B, et al. Smoking history and lung carcinoma: KRAS mutation is an early hit in lung adenocarcinoma development. *Lung Cancer*. 2012;75(2):156–160. doi:10.1016/j.lungcan.2011.07.013.
13. Ihle NT, Byers LA, Kim ES, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst*. 2012;104(3):228–239. doi:10.1093/jnci/djr523.
14. Skoulidis F, Byers LA, Diao L, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov*. 2015;5(8):860–877. doi:10.1158/2159-8290.Cd-14-1236.
15. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 2018;8(7):822–835. doi:10.1158/2159-8290.Cd-18-0099.
16. Reck M, Carbone DP, Garassino M, et al. Targeting KRAS in non-small-cell lung cancer: recent progress and new approaches. *Ann Oncol*. 2021;32(9):1101–1110. doi:10.1016/j.annonc.2021.06.001.
17. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *New Eng J Med*. 2021;384(25):2371–2381. doi:10.1056/NEJMoa2103695.
18. Willén L, Berglund A, Bergström S, et al. Educational level and management and outcomes in non-small cell lung cancer. A nationwide population-based study. *Lung Cancer*. 2019;131:40–46. doi:10.1016/j.lungcan.2019.03.004.
19. The Swedish Lung Cancer Registry Report 2012-2016 (Lungcancerrapporten, in Swedish). https://cancercentrum.se/globalassets/cancerdiagnoser/lunga-och-lungsack/kvalitetsregister/rapport/nlcr_rapport_tom2016_171120_publicera.pdf. Accessed November 9, 2022.
20. Finn SP, Addeo A, Dafni U, et al. Prognostic impact of KRAS G12C mutation in patients with NSCLC: results from the European Thoracic Oncology Platform Lungscape project. *J Thoracic Oncol*. 2021;16(6):990–1002. doi:10.1016/j.jtho.2021.02.016.
21. Hallqvist A, Enlund F, Andersson C, et al. Mutated KRAS is an independent negative prognostic factor for survival in NSCLC stage III disease treated with high-dose radiotherapy. *Lung Cancer Int*. 2012;2012. doi:10.1155/2012/587424.
22. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(9):911–919. doi:10.1200/jco.2017.76.7293.
23. Cui W, Franchini F, Alexander M, et al. Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer. *Lung Cancer*. 2020;146:310–317. doi:10.1016/j.lungcan.2020.06.030.
24. El Osta B, Behera M, Kim S, et al. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: The lung cancer mutation consortium experience. *J Thor Oncol*. 2019;14(5):876–889. doi:10.1016/j.jtho.2019.01.020.
25. Sebastian M, Eberhardt WEE, Hoffknecht P, et al. KRAS G12C-mutated advanced non-small cell lung cancer: A real-world cohort from the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). *Lung Cancer*. 2021;154:51–61. doi:10.1016/j.lungcan.2021.02.005.
26. Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of immune checkpoint inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC). *J Thor Oncol*. 2019;14(6):1095–1101. doi:10.1016/j.jtho.2019.01.011.
27. Kim JH, Kim HS, Kim BJ. Prognostic value of KRAS mutation in advanced non-small-cell lung cancer treated with immune checkpoint inhibitors: A meta-analysis and review. *Oncotarget*. 2017;8(29):48248–48252. doi:10.18632/oncotarget.17594.
28. Morgensztern D, Waqar S, Subramanian J, et al. Improving survival for stage IV Non-small cell lung cancer: a surveillance, epidemiology, and end results survey from 1990 to 2005. *J Thor Oncol*. 2009;4(12):1524–1529. doi:10.1097/JTO.0b013e3181ba3634.
29. Cramer-van der Welle CM, Verschueren MV, Tonn M, et al. Real-world outcomes versus clinical trial results of immunotherapy in stage IV non-small cell lung cancer (NSCLC) in the Netherlands. *Sci Rep*. 2021;11(1):6306. doi:10.1038/s41598-021-85696-3.
30. Scheffler M, Ihle MA, Hein R, et al. K-ras mutation subtypes in NSCLC and associated Co-occuring mutations in other oncogenic pathways. *J Thor Oncol*. 2019;14(4):606–616. doi:10.1016/j.jtho.2018.12.013.
31. Spira AI, Tu H, Aggarwal S, et al. A retrospective observational study of the natural history of advanced non-small-cell lung cancer in patients with KRAS p.G12C mutated or wild-type disease. *Lung Cancer*. 2021;159:1–9. doi:10.1016/j.lungcan.2021.05.026.
32. Wahl SGF, Dai HY, Emdal EF, et al. The prognostic effect of KRAS mutations in non-small cell lung carcinoma revisited: A Norwegian Multicentre Study. *Cancers*. 2021;13(17):4294. doi:10.3390/cancers13174294.
33. Liu SY, Sun H, Zhou JY, et al. Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients. *Biomark Res*. 2020;8:22. doi:10.1186/s40364-020-00199-z.
34. Ryberg D, Hewer A, Phillips DH, et al. Different susceptibility to smoking-induced DNA damage among male and female lung cancer patients. *Cancer Res*. 1994;54(22):5801–5803.
35. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. *Clin Cancer Res*. 2012;18(22):6169–6177. doi:10.1158/1078-0432.Ccr-11-3265.
36. Radkiewicz C, Dickman PW, Johansson ALV, et al. Sex and survival in non-small cell lung cancer: A nationwide cohort study. *PLOS ONE*. 2019;14(6). doi:10.1371/journal.pone.0219206.
37. Wheatley-Price P, Blackhall F, Lee SM, et al. The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials. *Ann Oncol*. 2010;21(10):2023–2028. doi:10.1093/annonc/mdq067.
38. Conforti F, Pala L, Bagnardi V, et al. Sex-Based Heterogeneity in response to lung cancer immunotherapy: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2019;111(8):772–781. doi:10.1093/jnci/djz094.
39. Arbour KC, Jordan E, Kim HR, et al. Effects of Co-occurring genomic alterations on outcomes in patients with KRAS-mutant non-small cell lung cancer. *Clin Cancer Res*. 2018;24(2):334–340. doi:10.1158/1078-0432.Ccr-17-1841.
40. Aredo JV, Padda SK, Kunder CA, et al. Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes. *Lung Cancer*. 2019;133:144–150. doi:10.1016/j.lungcan.2019.05.015.
41. Christensen TD, Spindler KL, Palshof JA, et al. Systematic review: brain metastases from colorectal cancer–Incidence and patient characteristics. *BMC Cancer*. 2016;16:260. doi:10.1186/s12885-016-2290-5.
42. Rabbie R, Ferguson P, Wong K, et al. The mutational landscape of melanoma brain metastases presenting as the first visceral site of recurrence. *Br J Cancer*. 2021;124(1):156–160. doi:10.1038/s41416-020-01090-2.
43. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer*. 2015;88(1):108–111. doi:10.1016/j.lungcan.2015.01.020.
44. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419–425. doi:10.1200/jco.2011.38.0527.
45. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv192–iv237. doi:10.1093/annonc/mdy275.
46. Schuler M, Wu YL, Hirsh V, et al. First-Line Afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thor Oncol*. 2016;11(3):380–390. doi:10.1016/j.jtho.2015.11.014.
47. Wardak Z, Choy H. Improving treatment options for brain metastases from ALK-positive non-small-cell lung cancer. *J Clin Oncol*. 2016;34(34):4064–4065. doi:10.1200/jco.2016.69.9587.
48. Page S, Milner-Watts C, Perna M, et al. Systemic treatment of brain metastases in non-small cell lung cancer. *Eur J Cancer*. 2020;132:187–198. doi:10.1016/j.ejca.2020.03.006.
49. Hendriks LEL, Henon C, Auclin E, et al. Outcome of patients with non-small cell lung cancer and brain metastases treated with checkpoint inhibitors. *Journal of Thoracic Oncology*. 2019;14(7):1244–1254. doi:10.1016/j.jtho.2019.02.009.
50. Lauko A, Kotecha R, Barnett A, et al. Impact of KRAS mutation status on the efficacy of immunotherapy in lung cancer brain metastases. *Sci Rep*. 2021;11(1):18174. doi:10.1038/s41598-021-97566-z.