Title	Patient characteristics and treatment of non-small cell lung cancer (NSCLC) patients – a Danish nationwide registry study
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Research Question and Objectives	Primary Objective: - To estimate overall survival (OS) of patients with locally advanced or metastatic NSCLC Secondary Objectives: - To describe KRAS testing uptake in patients with locally advanced or metastatic NSCLC - To estimate the prevalence of the KRAS G12C mutation in patients with locally advanced or metastatic NSCLC - To characterize patients with locally advanced or metastatic NSCLC in terms of demographics, clinical characteristics, tumour characteristics, treatment history, and genetic mutation profile
Country(ies) of Study	Denmark
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Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Not applicable
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1. ABSTRACT

- **Title**

Patient characteristics and treatment of non-small cell cancer (NSCLC) patients – a Danish nationwide registry study

- **Keywords**

Non-small cell lung cancer (NSCLC), Kirsten rat sarcoma viral oncogene homolog DNA with G12C mutation at the protein level (*KRAS* G12C*),* overall survival (OS)

- **Rationale and Background**

RAS-driven cancers have distinct properties that depend on both the specific mutation as well as the tissue type. The use of targeted therapies for actionable alterations, *EGFR*, *ALK*, *ROS-1,* and *BRAF* has shown high clinical efficacy, whereas there have been no effective therapies for NSCLC patients harbouring *KRAS* mutations (Renaud et al, 2016; Nadal et al, 2014; Ihle et al, 2012) leaving a high unmet medical need in these patients.

Recent advances have led to the development of *KRAS* G12C inhibitors such as, AMG510 (clinicaltrials.gov identifier NCT03600883) and MRTX849 (clinicaltrials.gov identifier NCT03785249). Preliminary clinical results demonstrate safety and clinical activity (Hallin et al, 2020; Canon et al, 2019). Given that there are no approved targeted therapies for advanced (locally advanced or metastatic) NSCLC patients with *KRAS* G12C in routine clinical setting, patient characteristics, treatment patterns and clinical outcomes have not been well-characterized as they are generally assessed within a treatment group of patients with unknown driver mutations. To date, there is limited data on characterization of patients with metastatic NSCLC in routine clinical practice in Denmark in terms of *KRAS* mutation status, treatment patterns and survival outcomes (Mellema et al, 2015).

The purpose of this study was to provide real world evidence on patient characteristics, genetic mutation profile, treatment patterns, and survival outcomes in the routine clinical setting in Denmark. Results will characterize the *KRAS* G12C mutated advanced NSCLC patient population and inform on the eligibility for treatment with the new *KRAS* G12C inhibitors if they become available in the future.

- **Research Question and Objectives**

Characterize advanced NSCLC patients and estimate overall survival (OS) according to *KRAS* mutation pattern

- **Study Design**

Population-based cohort study in Denamrk

- **Setting**

The source population was record-linkage data between the Danish Lung Cancer Register (DLCR), the Danish National Patient Registers (DNPR), the Danish Pathology Register (DPR), the Danish Civil Registration System, the Danish Prescription Registry, the National Laboratory Database Register, the National Health Insurance Service Register, the Danish Education Register and the Danish Income Statistics Register.

- **Subjects and Study Size, Including Dropouts**

Adults (aged ≥18 years) diagnosed with advanced NSCLC between 1 January 2018 to 30 June 2021.

A total of 17362 adult patients were diagnosed with incident NSCLC of whom 7440 (42.8%) patients with advanced NSCLC were eligible for the analyses.

- **Variables and Data Sources**

The source population is record-linkage data between Danish registers as described above in Setting. Variables included age, sex, smoking history, clinical and treatment related characteristics, presence of comutations and mutational burden.

- **Results**

Among all patients with NSCLC (N=17362), 7440 patients (42.8%) had evidence of advanced disease. Of the 2969 patients (40.0%) had a known *KRAS* test result at diagnosis or before start of line of treatment (LOT)1; 328 (11.0%) were *KRAS* G12C and included in the G12C cohort and 1185 (40.0%) were *KRAS/EGFR/ALK* wild type and included in the Triple WT cohort.

The prevalence of *KRAS* G12C mutation among patients with known *KRAS* test result was 11.0%.

Of the 7440 patients with advanced NSCLC, 2979 patients (40.0%) did not have evidence of receiving systemic treatment; similarly 35.7% of the 328 G12C and 39.0% of the 1185 Triple WT patients did not have evidence of receiving systemic treatment. During the study period, 60.0% of all advanced NSCLC patients received at least 1 line of systemic treatment and approximately one-fifth (23.8%) more than 1 line of therapy. Among the 328 patients with G12C, 64.3% had 1 line of therapy and 19.2% received 2 or more lines of therapy.

Median OS from NSCLC diagnosis, accounting for immortal time bias, was 7.1 months (95% CI: 5.9, 9.0) for the G12C cohort and 7.3 months (95% CI: 6.3, 8.1) for the Triple WT cohort; from the start of LOT1 14.0 months (95% CI: 10.3, 19.8) for G12C and 12.0 months (95% CI: 11.1, 13.8) for Triple WT; and from the start of LOT2 10.9 months (95% CI: 8.0, NE [Non Estimable]) for G12C and 9.7 months (95% CI: 8.4, 12.1) for Triple WT.

- **Discussion**

Results from this study highlight poor treatment outcomes for advanced NSCLC patients during the study period. Median OS for G12C patients was 7.1 months (95% CI: 5.9, 9.0) from the date of diagnosis accounting for immortal time bias. Furthermore, approximately 36% of G12C patients in this study did not have evidence of receiving any systemic treatment highlighting further the need for targeted therapies.

- **Marketing Authorization Holder(s)**

Not applicable

- **Names and Affiliations of Principal Investigators**

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Copenhagen Phase 4 Unit

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ALK	anaplastic lymphoma kinase
BRAF	B-Raf proto-oncogene
CI	confidence interval
DLCR	Danish lung cancer register
DNPR	Danish national patient register
DPR	Danish pathology register
EGFR	Epidermal growth factor receptor
G12C	glycine 12 to cysteine
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRAS G12C	Kirsten rat sarcoma viral oncogene homolog DNA with G12C mutation
LOT	line of treatment
NE	non estimable
NSCLC	non-small cell lung cancer
OS	overall survival
RAS	rat sarcoma viral oncogene homolog
ROS-1	proto-oncogene tyrosine-protein kinase
WT	Wild type

3. INVESTIGATORS

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4. OTHER RESPONSIBLE PARTIES

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