Summary Table of Study Protocol

Title	Patient characteristics and treatment of non-small cell cancer (NSCLC) patients – a Danish nationwide registry study
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Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	Primary Objective: 1. To estimate overall survival (OS) of patients with locally advanced or metastatic NSCLC Secondary Objectives: 2. To describe *KRAS* testing uptake in patients with locally advanced or metastatic NSCLC 3. To estimate the prevalence of the *KRAS* G12C mutation in patients with locally advanced or metastatic NSCLC 4. To characterize patients with locally advanced or metastatic NSCLC in terms of demographics, clinical characteristics, tumor characteristics, treatment history, and genetic mutation profile
Country(ies) of Study	Denmark
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Marketing Authorization Holder

Marketing authorization holder(s)	NA
MAH Contact	NA

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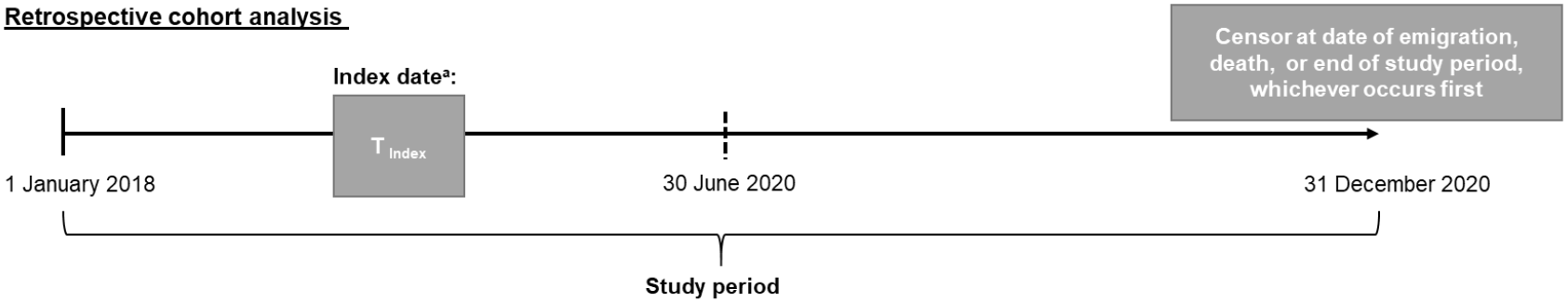
Investigator's Agreement

I have read the attached protocol entitled "Patient characteristics and treatment of non-small cell cancer (NSCLC) patients – a Danish nationwide registry study", dated 11 March 2021, and agree to abide by all provisions set forth therein.

Signature

Name of Investigator Date (DD Month YYYY)

Study Design Schema



Patient eligibility: Adults aged ≥18 years diagnosed with locally advanced (Stage IIIB/C) or metastatic (Stage IV) NSCLC between 1 January 2018 to 30 June 2020 in Denmark will be included.

[a]Time of Index date (T_{index}):
T_{index} will vary depending on the specific analysis. For example, T_{index} could be date of newly metastatic NSCLC diagnosis or start date of line of treatment (LOT) (i.e. date of first LOT will differ from date of 2nd LOT). T_{index} can occur at any timepoint during the study period (1 January 2018 to 31 December 2020) following locally advanced or metastatic NSCLC diagnosis.

Follow-up: Data on patients will be collected starting from date of locally advanced or metastatic NSCLC diagnosis to date of emigration, death, or end of study period (i.e. 31 December 2020), whichever occurs first.

1. Table of Contents

CCI

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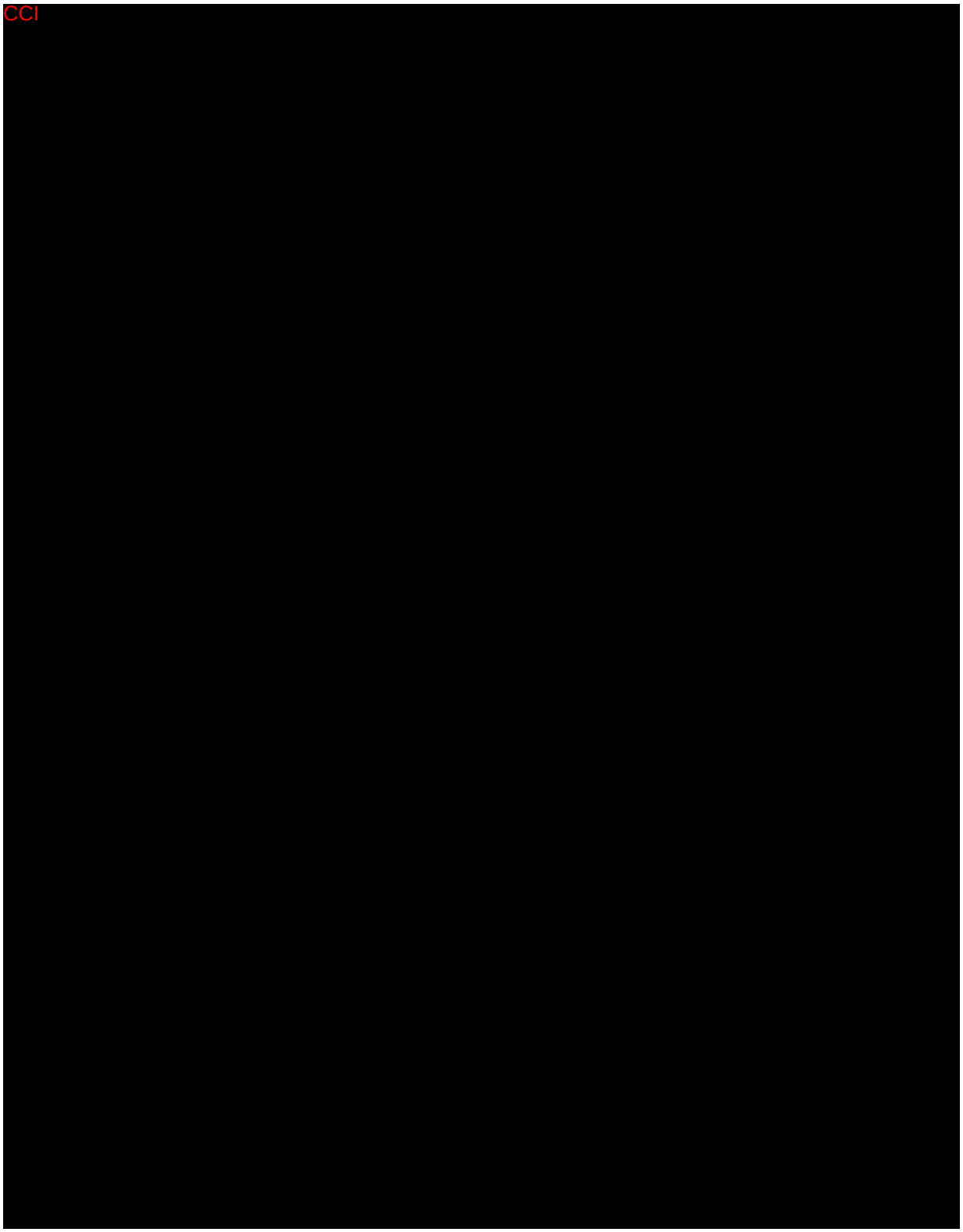

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2. List of Abbreviations

Abbreviations	Full names
CI	Confidence interval
DLCG	Danish Lung Cancer Group
DLCR	Danish Lung Cancer Register
DNPR	Danish National Patient Register
DPR	Danish Pathology Register
EC	Ethics Committee
LOT	Line of treatment
NSCLC	Non-small cell lung cancer
OS	Overall survival
SAP	Statistical Analysis Plan
TFL	Tables, Figures and Listings
TTNT	Time to next treatment
TTP	Time to progression

3. Responsible Parties

Role	**Contact Details**
Sponsor	Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320 United States
Principal Investigators	PPD Chief Physician Copenhagen Phase 4 Unit

4. Abstract

- **Study Title**

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

– **Study Background and Rationale**

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* have shown high clinical efficacy, whereas, there have been no effective therapies for NSCLC patients harboring *KRAS* mutations and outcomes are poorer (Renaud et al, 2016a; Nadal et al, 2014; Ihle et al, 2012), leaving a high unmet

medical need in these patients. Platinum-based combination therapy and immunotherapy (PD1/PDL1 inhibitors) are standard treatment in first-line setting, however, the large majority of patients will progress (Bluthgen and Besse, 2015) and PD1/PDL1 inhibitors are not yet fully used as they have been recently approved. To date, the only approved second-line treatments for advanced NSCLC without targetable oncogenic drivers are docetaxel, pemetrexed, the EGFR inhibitor (TKI) erlotinib (Bluthgen and Besse, 2015) and PD1/PDL1 inhibitors. Of the therapies, standard of care treatment with docetaxel as a single agent chemotherapy or in combination with antiangiogenic drugs have been available for more than two decades (EMA approval, November 1995), whereas the other therapies have been approved more recently.

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; Hong et al, 2020; Canon et al, 2019). Given that there are no approved targeted therapies for 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. In order to comprehensively understand the natural history and prognosis of these *KRAS* G12C mutated locally advanced and metastatic NSCLC patients, the objective of this retrospective cohort study is 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 locally advanced and metastatic NSCLC patient population and inform on the eligibility for treatment with the new *KRAS* G12C inhibitors if they become available in the future.

– **Study Feasibility and Futility Considerations**

Analyses of real-world treatment patterns for NSCLC patients have been conducted in previous Danish record-linkage studies (Danish Lung Cancer Registry, 2018; Jeppesen et al, 2018; Iachina et al, 2017; Miret et al, 2017). The planned analyses are feasible.

– **Research Question and Objective(s)**

Objectives	Endpoints
Primary	
• To estimate overall survival (OS) of patient with locally advanced or metastatic NSCLC	• OS
Secondary	
• To describe *KRAS* testing uptake in patients with locally advanced or metastatic NSCLC	• Proportion of patients with locally advanced or metastatic NSCLC who are tested for *KRAS*
• To estimate the prevalence of *KRAS* G12C mutation in patients with locally advanced or metastatic NSCLC	• *KRAS* G12C mutation status
• To characterize patients with locally advanced or metastatic NSCLC in terms of demographics, clinical characteristics, tumor characteristics, treatment history, and genetic mutation profile	• Demographics, clinical characteristics, tumor characteristics, treatment history (eg, line of therapy (LOT), type of treatment and time-to-next treatment (TTNT)) and genetic mutation profile,

– **Hypothesis(es)/Estimation**
The objectives of the study are descriptive. No formal hypothesis will be tested.

- **Study Design/Type**

A retrospective cohort study of locally advanced or metastatic NSCLC patients in a Danish nationwide cohort.

– **Study Population or Data Resource**

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

- **Summary of Patient Eligibility Criteria**

Inclusion criteria

- Adults aged ≥ 18 years at time of NSCLC diagnosis
- Diagnosed with incident locally advanced (Stage IIIB/C) or metastatic (Stage IV) NSCLC between 1 January 2018 to 30 June 2020.

Exclusion criteria

- Patients who immigrated to Denmark less than one year before NSCLC diagnosis
- Patients initially diagnosed with Stage I-IIIa NSCLC and progressed to advanced NSCLC during the study period will be excluded

- **Follow-up**

The study period will span from 1 January 2018 to 31 December 2020. Data on patients will be collected starting from date of locally advanced or metastatic NSCLC diagnosis until date of emigration, death or end of the study period (ie, 31 December 2020), whichever occurs first.

The study period may be modified subject to availability of data at time of primary analysis. At the minimum, there will be data available up to 31 December 2019.

- **Variables**
  - ***Outcome Variable(s)***
    - Overall survival (OS): OS will be defined as the time from a given index date (ie, locally advanced or metastatic NSCLC diagnosis or start date of treatment) to death. Patients without evidence of death will be censored on date of emigration or at the end of the study period (ie, 31 December 2020).
    - *KRAS* testing status
    - *KRAS* G12C mutation status
  - ***Exposure Variable(s)***
    - Treatment type: chemotherapy, targeted therapy, immunotherapy, other
    - Lines of therapy (LOT): LOT1 will be defined from the start of the first systemic therapy drug(s) to the completion of the first systemic therapy drug(s). Detailed guidelines on defining completion of LOT will be provided in the statistical analysis plan.
  - ***Other Covariate(s)***
    - Key covariates include: demographics, clinical characteristics, tumor characteristics, treatment history, genetic mutation profile

- **Study Sample Size**

Sample size estimates are based on projected number of patients meeting the study eligibility criteria. As this study is descriptive in nature and no hypothesis are being tested, power calculations have not been performed.

Assuming 3900 NSCLC patients are diagnosed annually, of which 2649 patients are locally advanced or metastatic from 2018 to 2020 (Danish Lung Cancer Registry, 2018) (, there will be approximately 8000 locally advanced or metastatic NSCLC patients eligible for analysis. One-year survival rates ranges from 61.6% for Stage IIIB to 25.8% for Stage IVB lung cancers (Danish Lung Cancer Registry, 2018). With a sample size of 8000 patients, this would give us sufficient precision to estimate the proportion of patients with a death outcome with estimated confidence intervals (CIs) as presented in Table 1.

- **Data Analysis**

OS is the primary outcome. Non-parametric methods will be used to estimate OS. To describe time-to-event (OSand TTNT), Kaplan-Meier (KM) curves will be plotted, and survival probabilities 95% confidence intervals (CIs) will be presented. The estimated survival probabilities for OS and corresponding 95% CIs will be presented for patients at 6 months and 12 months. Median OS and corresponding 95% CI will also be presented. For time-to-event analyses, patients will be censored at date of emigration, death, or end of study period (ie, 31 December 2020), whichever occurs first. For OS analyses, the index date will be determined by the start date of the type of treatment or start date of LOT, depending on the analysis.

The proportion of biomarker testing rates and prevalence of *KRAS* G12C mutation will be presented.

Patient demographics, clinical characteristics, tumor characteristics, treatment patterns and genetic mutation profile will be described overall for all locally advanced or metastatic NSCLC patients and according to *KRAS* status using summary statistics.

5. Amendments and Updates

Not applicable.

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Globally, lung cancer is the most frequent in males and the third most frequent in females after cancer of the breast and colorectum (Bray et al, 2018). In 2018, there was

Approval Signatures

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