Summary Table of Study Protocol

Title	**RAStik:** A **R**etrospective Cohort **A**nalysis of **S**urvival and **T**reatment Outcomes of Docetaxel in ***K****RAS* G12C Mutated Locally Advanced or Metastatic NSCLC
Protocol version identifier	20190411
Date of last version of the protocol	Not applicable
EU Post Authorization Study (PAS) Register No	Not applicable
Active Substance	Not applicable
Medicinal Product	Not applicable
Device	Not applicable
Product Reference	Not applicable
Procedure Number	Not applicable
Joint PASS	No

Research Question and Objectives	Primary objectives • To evaluate the real-world efficacy of docetaxel (monotherapy or combination) in ≥second-line treatment of patients with *KRAS* G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) • To estimate overall survival (OS) and real-world progression-free survival (rwPFS) survival in patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC treated in ≥second-line with docetaxel (monotherapy or combination) Secondary objectives • To estimate the prevalence of *KRAS* G12C mutation in patients with locally advanced or metastatic NSCLC • To characterize patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC who were treated with docetaxel (monotherapy or combination) in ≥second-line, in terms of demographics, clinical characteristics, tumor characteristics, treatment patterns and genetic mutation profile • To evaluate real-world efficacy and survival by type of treatment (NOT docetaxel) in patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC patients Exploratory objectives • To describe the effect of chemotherapy (with or without immunotherapy) dose intensity on patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC, dose delays, dose reductions, dose interruptions, dose intensity and their association with real-world treatment efficacy • To describe the genetic mutation profile of *KRAS* G12C mutated locally advanced or metastatic NSCLC at diagnosis, before and after systemic treatment, and at time of disease progression, if re-biopsied • To describe risk factors associated with survival in *KRAS* G12C mutated locally advanced or metastatic NSCLC patients
Country(ies) of Study	Germany

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Marketing Authorization Holder

Marketing authorization holder(s)	Not applicable
MAH Contact	Not applicable

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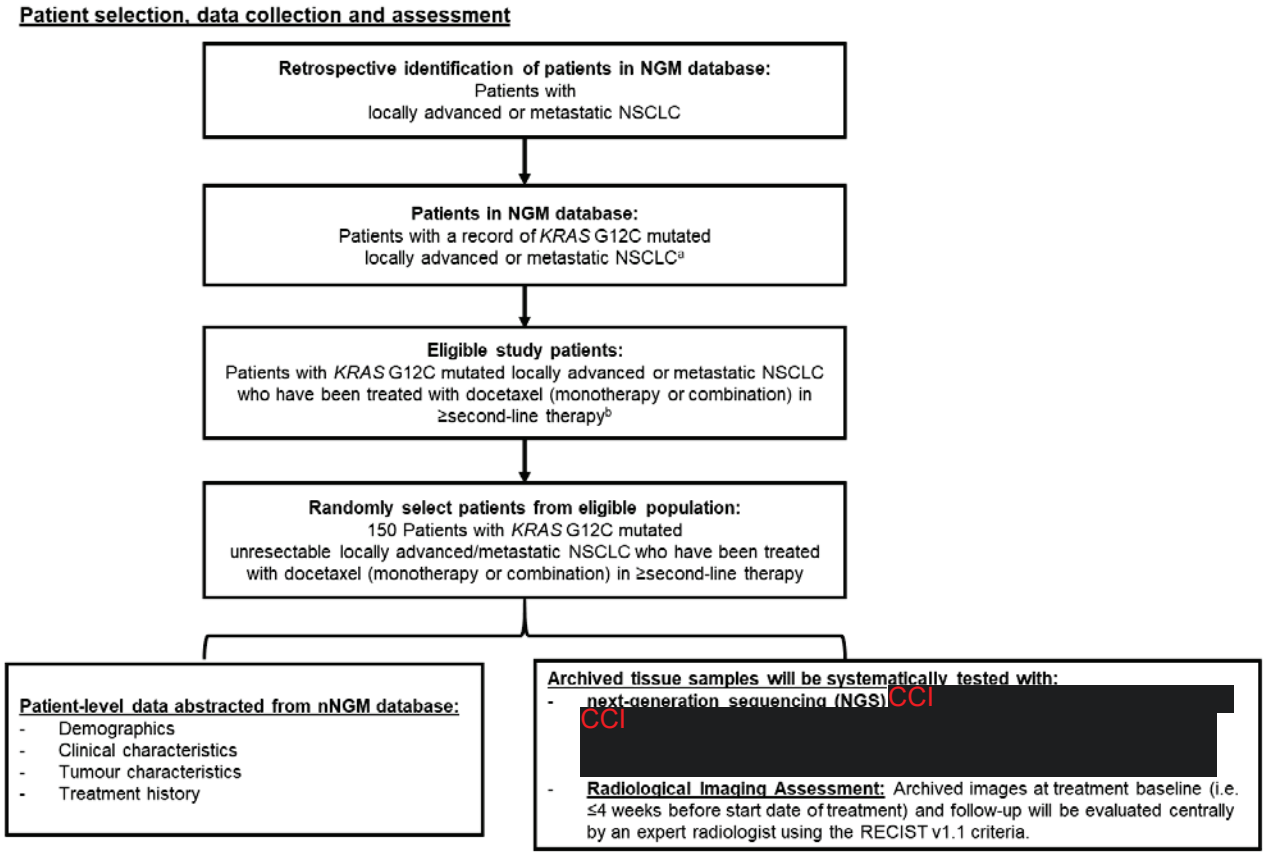
Investigator's Agreement

I have read the attached protocol entitled "RAStik: A retrospective observational cohort study of treatment outcomes of docetaxel in *KRAS* G12C-mutated non-small cell lung cancer", dated 3 September 2020, and agree to abide by all provisions set forth therein.

Signature

Name of Investigator Date (DD Month YYYY)

Study Design Schema

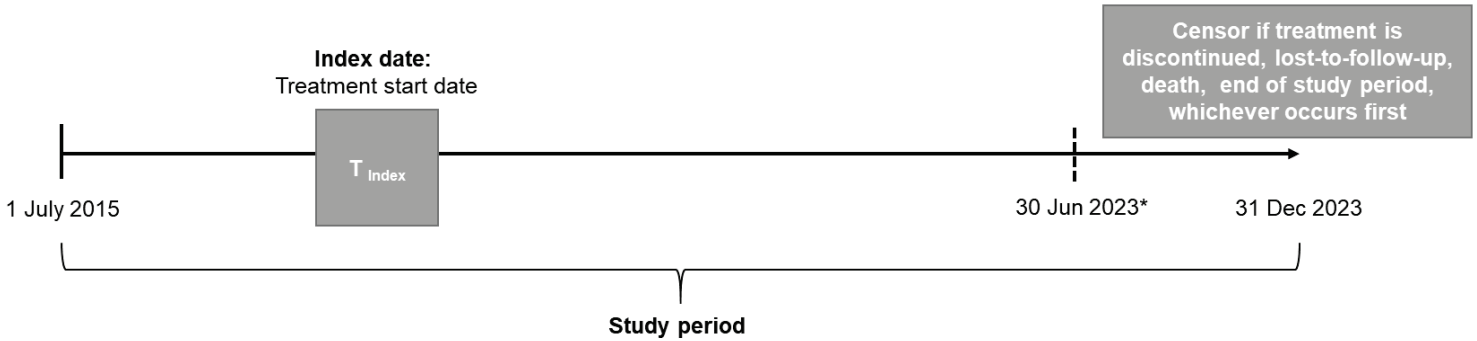


Abbreviations: NGM, National Network Genomic Medicine; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing

[a] Prevalence of *KRAS* G12C in locally advanced or metastatic NSCLC.

[b] Eligible patients are adults (aged ≥18) patients diagnosed between 1 July 2015 and 30 June 2019 with pathologically documented locally advanced or metastatic NSCLC from the Cologne center; have a record of treatment with docetaxel (monotherapy or combination) in ≥second-line (e.g. 2nd line, 3rd line, 4th line, or 4th line+); have a molecular test result of *KRAS* G12C somatic mutation recorded before start date of treatment with docetaxel; have formalin-fixed, paraffin-embedded (FFPE) tumor samples with adequate material available for biomarker testing (i.e., >10% of tumor cells are available on sample) that was archived before start date of treatment with docetaxel; have CT-Scan or MRI documentation of measurable disease at treatment baseline for docetaxel (i.e., ≤4 weeks before start date of treatment); and have documented consent that their medical data and residual tissue samples can be used for research purposes

Retrospective cohort analysis



*Eligible patients are adults (aged ≥18) patients diagnosed with locally advanced or metastatic NSCLC between 1 July 2015 and 30 June 2023 in ESME-AMLC database. Those who have a history of treatment with chemotherapy, immunotherapies, targeted therapies, or anti-angiogenic agents as part of a clinical trial will be excluded

1. Table of Contents

CCI

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[redacted]

2. List of Abbreviations

Abbreviations	Full names
CCI	Charlson Comorbidity Index
CI	Confidence interval
CT	Computerized tomography
DCR	Disease control rate
DOR	Duration of overall response
DOT	Duration of treatment
CR	Complete response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin fixed, paraffin embedded
FISH	Fluorescence in situ hybridization
GM-CSF	Granulocyte-macrophage colony-stimulating factor
ICJME	International Committee of Medical Journal Editors
IDAT	Date of birth
IV	Intravenous
KM	Kaplan-Meier
LOT	Line of treatment
MDAT	Medical data
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NGS	Next generation sequencing
NGM	Network Genomic Medicine
nNGM	National Network Genomic Medicine
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PD-1/PD-L1	Programmed cell death protein 1
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
rwORR	Real-world objective response rate

Abbreviations	Full names
rwPFS	Real-world progression free survival

Abbreviations	Full names
SAP	Statistical Analysis Plan
SD	Standard deviation
SD	Stable disease
SE	Standard error
SOP	Standard Operating Procedures
Tc-99m	technetium-99m
TTNT	Time to Next Therapy
TTP	Time to Progression
UICC	Union for International Cancer Control

3. Responsible Parties

Role	Contact Details
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4. Abstract

- **Study Title**

RAStik: A retrospective cohort analysis of survival and treatment outcomes of docetaxel in *KRAS* G12C mutated locally advanced or metastatic NSCLC

- **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, CCI CCI have shown high clinical efficacy, whereas, there have been no effective therapies for non-small cell lung cancer (NSCLC) patients harboring Kirsten rat sarcoma viral oncogene homolog (*KRAS)* mutations and thereby outcomes poorer (Renaud et al, 2016a; Nadal et al, 2014; Ihle et al, 2012), leaving a high unmet medical need in these patients. However, 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. AMG 510 is an irreversible small molecule inhibitor of KRAS protein with a G12C mutation at the protein level that is being developed to treat patients with solid tumors, including NSCLC, with the KRAS G12C mutation (Canon et al, 2019). It irreversibly locks KRAS G12C in an inactive state and is highly selective (>1000-fold) in inhibition of mutant over wild-type KRAS. As a result, it blocks the survival and proliferation and differentiation of tumor cells with KRAS G12C mutations; and has led to the regression of KRAS G12C tumors and improved anti-tumor efficacy besides chemotherapy and other agents. MRTX849 has a similar mechanism of action of inhibiting KRAS-dependent signaling (Hallin et al, 2020).

Currently, there are no targeted therapies for *KRAS* G12C mutated NSCLC used in routine clinical setting, and patient characteristics, treatment patterns and clinical outcomes have not been well-characterized. 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 observational cohort study is to provide real world evidence on patient characteristics, genetic mutation profile, treatment patterns, observational treatment responses according to RECIST v1.1, and survival outcomes in the routine clinical setting in Germany. Results will contextualize 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.

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

Objectives	**Endpoints**
Primary	
• To evaluate the real-world efficacy of docetaxel (monotherapy or combination) in ≥second-line treatment of patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC	• real-world Objective Response Rate (rwORR as defined by complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to Response evaluation criteria in solid tumors (RECIST) guideline version 1.1 • Duration of overall response (DOR) • Disease control rate (DCR) • Duration of Treatment (DOT) • Time to Next Therapy (TTNT) • Time to Progression (TTP)
• To estimate OS and rwPFS survival in patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC treated in ≥second-line with docetaxel (monotherapy or combination)	• Overall survival (OS) • real-world Progression-free survival (rwPFS)

Objectives	Endpoints
Secondary	
• To estimate the prevalence of *KRAS* G12C mutation in patients with locally advanced or metastatic NSCLC	• Prevalence of *KRAS* G12C mutation
• To characterize patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC who were treated with docetaxel (monotherapy or combination) in ≥second-line, in terms of demographics, clinical characteristics, tumor characteristics, treatment patterns and genetic mutation profile	Patient Characteristics • Demographics (age, sex, and smoking status) • Clinical characteristics (ECOG performance status, comorbidities, history of other malignancies) • Tumor characteristics (tumor site, histology, grade of tumor and sites of metastases, if applicable, and PD-L1 expression status) • Treatment history (chemotherapy, targeted therapy, immunotherapy, anti-angiogenic therapy, concomitant medications and other) • Genetic mutation profile according to genes detected by next-generation sequencing (NGS) CCI [redacted]
• To evaluate real-world efficacy and survival by type of treatment (NOT docetaxel) in patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC patients	• rwORR (CR, PD, SD, and PD) according to RECIST v1.1 • DOR, DCR, DOT, TTNT, TTP • OS and rwPFS

Objectives	Endpoints
Exploratory	
• To describe the effect of chemotherapy (with or without immunotherapy) dose intensity on patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC, dose delays, dose reductions, dose interruptions, dose intensity and their association with real-world treatment efficacy	• Proportion of patients with dose delays, dose reductions, missing doses, and relative dose intensity • rwORR (CR, PD, SD, and PD) according to RECIST v1.1. • DOR, DCR, DOT, TTNT, TTP • OS and rwPFS
• To describe the genetic mutation profile of *KRAS* G12C mutated locally advanced or metastatic NSCLC at diagnosis, before and after systemic treatment, and at time of disease progression, if re-biopsied	• Frequency of genetic mutation profile before and after systemic treatment
• To describe risk factors associated with survival in *KRAS* G12C mutated locally advanced or metastatic NSCLC patients	• OS and rwPFS

- **Hypothesis(es)/Estimation**

The objectives of the study are descriptive. No formal hypothesis will be tested.

- **Study Design/Type**

A retrospective observational cohort study of *KRAS* G12C mutated locally advanced or metastatic NSCLC patients treated in the Network Genomic Medicine (NGM) network will be conducted. Patients who have been treated with docetaxel (monotherapy or combination) in ≥second-line, have adequate tissue samples for biomarker testing archived before start date of docetaxel treatment and have computerized tomography (CT) scans or magnetic resonance imaging (MRI) available at treatment baseline for docetaxel (ie, ≤4 weeks before start date of treatment) will be eligible for study inclusion. CT/MRI scans available from baseline to 8 weeks ±2 weeks after treatment discontinuation (if available) will be eligible for evaluation centrally by an expert radiologist using the Response Evaluation Criteria for Solid Tumors (RECIST) guideline version 1.1 (Eisenhauer et al, 2009) to obtain real-world objective treatment response and disease control rate (DCR). According to German guidelines (Giesinger et al, 2019; Leitlinienprogramm Onkologie, 2018), CT/MRI scans for treatment evaluation are

normally performed at 6-8 weeks intervals. Scans eligible for evaluation will be those conducted every 8±2 weeks from treatment start date to 8±2 weeks after date of treatment discontinuation. Scans performed for reasons unrelated to treatment evaluation (eg, hospitalizations) will be excluded. Details of the selection of slides will be specified in the statistical analysis plan (SAP).

In the same way, other treatments (NOT docetaxel) that the patient received will also be analyzed if CT/MRI scans are available at treatment baseline (ie, ≤4 weeks before start date of treatment); and all scans available up to 8±2 weeks after treatment discontinuation will be reviewed with RECIST v1.1 to obtain real-world objective response and DCR. In addition, tissues samples will undergo systematic testing to detect genetic alterations using the NGS [redacted]. Clinical data on patient characteristics, tumor characteristics and treatment history recorded in the NGM database will also be extracted for data analysis.

- **Study Population or Data Resource**

The source population is the NGM database. The study period will span from 1 July 2015 to 31 December 2019.

- **Summary of Patient Eligibility Criteria**

Inclusion criteria

- Adult (aged ≥18) patients diagnosed between 1 July 2015 and 30 June 2019 with pathologically documented locally advanced or metastatic NSCLC from the Cologne center
- Have a record of treatment with docetaxel (monotherapy or combination) in ≥second-line (eg, 2nd line, 3rd line, 4th line, or 4th line+)
- Have a molecular test result of *KRAS* G12C somatic mutation recorded before start date of treatment with docetaxel
- Have FFPE tumor samples with adequate material available for biomarker testing (ie, >10% of tumor cells are available on sample) that was archived before start date of treatment with docetaxel
- Have CT-Scan or MRI documentation of measurable disease at treatment baseline for docetaxel (ie, ≤4 weeks before start date of treatment)
- Have documented consent that their medical data and residual tissue samples can be used for research purposes (see section 9.1)

Exclusion criteria

- Have a history of treatment with chemotherapy, immunotherapies, targeted therapies, or anti-angiogenic agents as part of a clinical trial

- **Follow-up**

Data on patients will be collected starting from date of locally advanced or metastatic NSCLC diagnosis until death, lost-to-follow-up, or end of study period (ie, 31 December 2019), whichever occurs first.

- **Variables**
  - ***Outcome Variable(s)***
    - real-world Objective Response Rate (rwORR) as defined by complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) according to RECIST guideline version 1.1
    - Duration of response (DOR)
    - Disease control rate (DCR)
    - Duration of Treatment (DOT)
    - Time to Next Therapy (TTNT)
    - Time to Progression (TTP)
    - Overall survival (OS)
    - real-world Progression free survival (rwPFS)
  - ***Exposure Variable(s)***
    - Treatment history, in terms of start and end dates, dose delays, dose reductions, dose intensity, reason for discontinuation (disease progression, drug intolerance, toxicity, completed course of treatment), and line of treatment (LOT)
    - Chemotherapy: gemcitabine/gemcitabine hydrochloride; pemetrexed; docetaxel; carboplatin; cisplatin; etoposide/etoposide phosphate; irinotecan/irinotecan hydrochloride; topotecan; vinorelbine tartrate; vinblastine sulfate; paclitaxel; Nab-paclitaxel, albumin bound; cetuximab; other
    - Targeted therapy: afatinib; cabozantinib; ceritinib; crizotinib erlotinib; gefitinib; alectinib; osimertinib; dabrafenib and trametinib; brigatinib; lorlatinib, necitumumab, cobimetinib, vemurafenib
    - Immunotherapy: nivolumab; pembrolizumab; duravalumab; atezolizumab; avelumab; pidilizumab; other
    - Anti-angiogenic agents: bevacizumab, nintendanib. ramucirumab
  - ***Other Covariate(s)***
    - Demographics
      - Age at advanced NSCLC diagnosis
      - Sex (male, female, unknown)

- Smoking status (never, former, current, not applicable) and if applicable, smoking quantity (pack-years)

- Clinical characteristics
  - ECOG performance status (0, 1, 2, 3, 4, Missing/Unknown)
  - PD-L1 tested (yes/no) and expression status, among tested (percent of positive tumor cells for the sample by PD-L1 staining/testing: $<1\%$, $1-<50\%$, $\geq 50\%$)
  - Comorbidities (yes, no, unknown) as defined by the Charlson Comorbidity Index (CCI) (Charlson et al, 1987): acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer, mild liver disease, mild to moderate diabetes, diabetes with chronic complications, hemiplegia or paraplegia, kidney disease, malignant tumors, moderate to serious liver disease, solid/metastatic tumor, AIDS
  - History of other malignancies

- Prior radiotherapy treatment
  - date of radiotherapy
  - body area irradiated (lymph nodes, lung, brain, other)
  - total dose of radiotherapy and fractions
  - curative intent/palliative

- Surgical history
  - Date of resection
  - Type of resection (pneumonectomy, lobectomy, segmentectomy, wedge resection, sleeve resection, other)

- Tumor characteristics
  - Date of primary NSCLC diagnosis
  - Tumor site (upper lobe, middle lobe, lower lobe; overlapping lesions of lung, lung not otherwise specified (NOS), trachea NOS)
  - Specimen laterality (right, left, NOS)
  - Lymphovascular invasion (not identified, lymphatic, arterial, venous, cannot be determined)
  - Histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or undifferentiated NSCLC; and mucinous vs. non-mucinous)
  - Grade of tumor (TNM staging and Stage III or IV), and if applicable, date of metastatic diagnosis and sites of metastases (adrenal, bone, liver, distant lymph node, other central nervous system, lung, other)
    - M1: distant metastasis
    - M1a: separate tumor nodules(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion

  - M1b: distant metastasis (in extrathoracic organs)
  - Date of tumor sample collected that was used to determine positivity for *KRAS* G12C
- Concomitant medications (opioids, GM-CSF and bone-targeted agents,)
- Tissue sample collection date to be used for biomarker testing
- Genetic mutation profile according to genes detected by NGS with CCI
CCI

- **Study Sample Size**

This study will evaluate real-world treatment efficacy (according to RECIST criteria) and survival outcomes for patients with *KRAS* G12C mutated locally advanced or metastatic NSCLC who have been treated with docetaxel (monotherapy or combination) in ≥second-line. The study size of 150 patients was based on the resource available for NGS testing. For this reason, 150 patients will be randomly selected from the sampling frame of all eligible *KRAS* G12C mutated locally advanced or metastatic NSCLC population who were treated with docetaxel (monotherapy or combination). Response rates of up to 20% in this population have been reported (Bluthgen and Besse, 2015). The expected precision for estimating the proportion of patients achieving an objective response, as assessed by the maximum half-width of the 95% CI, for a range of sample sizes and varying assumptions of rwORR of 5% to 20% are shown in section 8.5. For example, for a rwORR of 10% observed with 150 patients, the expected 95% CI is 5.7-16.0%. In estimation terms, a sample size of 100 patients would ensure that the half-width of the 95% CI for an observed rwORR of ≤ 20% would be no larger than 10 percentage points.

- **Data Analysis**

The primary outcomes are rwORR, OS and rwPFS. Non-parametric methods will be used to estimate OS and rwPFS. To describe time-to-event (rwORR, CR, PR, SD, PD, rwPFS, and OS), Kaplan-Meier (KM) curves will be plotted, and survival probabilities 95% confidence intervals (CIs) will be presented (eg, 6 months and 12 months). Median OS and rwPFS and 95% CI will be presented. Patients will be censored if treatment is discontinued, lost-to-follow-up, death, end of study period, whichever occurs first. Survival differences may be assessed for statistical significance using two-sided Log-Rank in Kaplan-Meier. The level of significance will be set at 0.05. For analyses of

rwORR and survival, the index date will be determined by the start date of the type of treatment or start date of LOT, depending on the analysis. If sufficient numbers are obtained, analyses may also be presented by subgroups (section 8.7.2.5.1)

Duration or time to events (DOR, DCR, TTNT, and TTP) will be summarized (mean, median, standard deviation, range).

The prevalence of *KRAS* G12C mutation-positive will be estimated when defining the eligible study population as shown in Study Design Schema.

Patient demographics, clinical characteristics, tumor characteristics, treatment patterns and genetic mutation profile among patients with locally advanced or metastatic NSCLC will be described using summary statistics (section 8.7.2.1). Treatment patterns based on the observed distribution of treatment administered, as well as the distribution of treatment types (ie, chemotherapies, targeted therapies, immunotherapy, anti-angiogenic therapies) will be described, overall and by LOT. Differences in patient characteristics may be assessed with t-tests for normally distributed continuous data, otherwise by means of non-parametric Mann-Whitney-U- and chi-squared test for categorical variables.

Proportion of patients experience dose delays, dose reductions and relative dose intensity; and genetic mutation profile before and after systemic treatment will be summarized.

To describe factors associated with time-to-event, a multivariate Cox model will be used.

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 an estimate of over two million new cases and 1.7 million deaths, representing 14% of all new cancer cases and 20% of cancer deaths (Miranda-Filho et al, 2019). The highest mortality rates can be found in industrialized countries such as those in North America and Europe. In Germany, lung cancer is the most common type of cancer in males and females with over 55,000 new cases diagnosed each year, which represents 25% of all cancer deaths and is the third most common cancer in females (Robert Koch Institute,