STUDY REPORT SYNOPSIS

Study report - Synopsis	
Study code	D5160R00005
Version	1.0
Date	09 May 2021

PANORAMA

Real World Molecular Testing, Treatment Patterns, and Clinical Outcomes in Patients with EGFR Mutation-Positive Locally Advanced or Advanced NSCLC

Milestones: Start of data collection (FPI): May 26, 2016
End of data collection (LPO): May 31, 2020

Phase of development: Not applicable – Observational [Patient Registry]

Sponsor: AstraZeneca

Author: [redacted]

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

The majority (50-60%) of patients with Epidermal Growth Factor Receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) acquire resistance to front-line EGFR-targeted tyrosine kinase inhibitors (TKIs) due to a T790M-mutation. At start of PANORAMA the standard of care among patients progressing following an EGFR-TKI therapy was platinum based doublet chemotherapy, which achieved response rates in the range of 20% to 35%. Osimertinib was the first approved third-generation TKI targeting T790M-mutant NSCLC. In a phase III trial, osimertinib showed significantly better response rates and progression-free survival than platinum therapy plus pemetrexed in patients who had progressed after first-line TKI (Mok et al., 2017).

Use of osimertinib after progression following EGFR-TKI therapy requires confirmation of a T790M mutation. The need for testing to determine the T790M mutation status and the resultant shift from a chemotherapy-based regimen to oral targeted therapy changed the standard of care and management practices in this treatment setting.

PANORAMA was designed to study the evolving real-world molecular testing and treatment patterns and associated physician reported outcomes including time to initiation of a new treatment among patients with EGFR mutation-positive locally advanced or advanced NSCLC who had progressed on/after TKI therapy.

Objectives:

The primary objectives of this study were to describe molecular testing and treatment patterns in patients with locally advanced or metastatic EGFR-positive NSCLC who had progressed on or after TKI treatment (primary study cohort) or in patients with de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC (secondary cohort). Further for patients assigned to the primary cohort associated clinical outcomes were explored.

Secondary objectives were to describe health care utilization patterns, treatment and biopsy related complications, rate of CNS metastases and associated treatments, and patient-reported health-related quality of life (HRQoL), using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13).

Study design:

PANORAMA was a non-interventional, prospective, observational cohort study including 80 study sites in Germany, 53 study sites actively recruiting patients either with EGFR mutation-positive locally advanced or metastatic NSCLC who had progressed on/after TKI therapy (primary study cohort) or patients diagnosed with de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC (secondary study cohort). Recruitment of patients started in May 2016. Patients were enrolled during a 37 months enrollment period and were followed from their study enrollment date until death, loss to follow-up, withdrawal of consent or study end date on May 31, 2020. There were no specific drug exposures or interventions being evaluated, as cohort eligibility (for both cohorts) is not exposure- but rather disease-based.

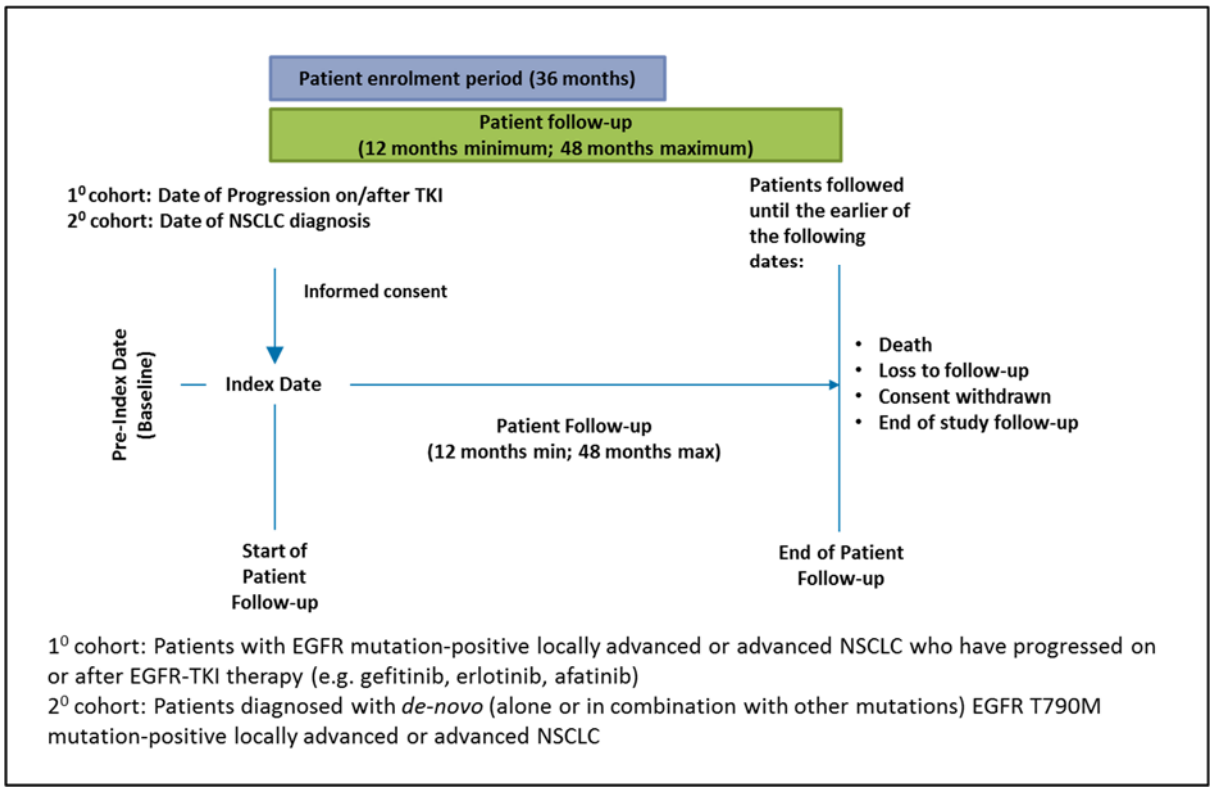

Figure 1: Schematic representation of study periods

Data source:

Data were collected (in parts prospectively) following enrollment in the study and entered in the electronic Case Report Form (eCRF). Baseline data and all information about e.g. treatments and molecular testing performed before enrollment were collected using patient medical records. The site investigator was responsible for ensuring that all the required data were collected and entered into the eCRF.

Study population:

According to the PANORAMA protocol, patients aged ≥ 18 years with locally advanced or metastatic NSCLC who have progressed on/after TKI therapy were included into the primary study cohort. The individual therapy decision for further lines of treatments was made by the treating physician. Patients should be included within 6 weeks after progression on/after TKI therapy but could also be included when progression has been more than 6 weeks before. Due to this, some patients have been included prospectively and some retrospectively.

Until database cut on May 31, 2020, 159 patients were enrolled in 53 sites in Germany. The primary study cohort includes 152 patients with EGFR mutation-positive locally advanced or metastatic NSCLC who have progressed on/after TKI therapy (i.e. gefitinib, erlotinib, afatinib). Additionally, the secondary cohort of 7 patients diagnosed with de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC was enrolled in this study. Due to small number of recruited patients into the secondary cohort, this final analysis will only focus on primary study cohort patients.

Inclusion criteria:

Patients had to comply with all the following criteria in order to be enrolled in one of the two patient cohorts as follows:

- Primary study cohort: Patients with prior confirmed EGFR mutation-positive locally advanced or metastatic NSCLC who have progressed on/after TKI therapy (i.e., gefitinib, erlotinib, afatinib)
- Secondary study cohort: Patients diagnosed with de-novo EGFR T790M mutation-positive locally advanced or metastatic NSCLC
  (de-novo T790M mutation can be alone or in combination with other mutations (e.g., L858R and T790M).

The specific study inclusion and exclusion criteria for both cohorts are described in the sections below:

Inclusion Criteria – Primary Study Cohort

- The inclusion criteria for the primary study cohort are as follows: Provision of written informed consent (patient consent should* be within 6 weeks of disease progression, defined as Index Date) (*not mandatory)
- Adult male or female subjects (according to age of majority/adulthood as defined by local regulations)
- Patients with prior confirmed EGFR mutation-positive (all mutations) locally advanced or metastatic NSCLC (Patients who developed resistance to a TKI due to any other phenotypic/histologic transformations (e.g., small-cell lung cancer, EMT) or other mutations (e.g., HER2, MET amplifications) at the index-date will be eligible for participation in this study as long as they have prior confirmed diagnosis of EGFR mutation-positive (all mutations) locally advanced or metastatic NSCLC)
- Patients who have progressed on/after TKI therapy (e.g., gefitinib, erlotinib or afatinib) within the patient selection period

Inclusion Criteria – Secondary Study Cohort

The inclusion criteria for the secondary study cohort are as follows:

- Provision of written informed consent (patient consent should* be within 6 weeks of NSCLC diagnosis, defined as Index Date)
  (*not mandatory)
- Adult male or female subjects (according to age of majority/adulthood as defined by local regulations)
- Patients diagnosed with *de-novo* EGFR T790M mutation-positive locally advanced or metastatic NSCLC during the patient selection period. The *de-novo* T790M mutation can be alone or in combination with other mutations (e.g., L858R and T790M).

Exclusion criteria – Primary and Secondary Study Cohorts:

Patients were not included in the study, if the following criterion was met:

- Enrollment in studies that prohibit any participation in this NIS

Statistical methods:

According to the observational plan and the pre-specified statistical analysis plan (SAP) all variables were analyzed in a descriptive manner. For continuous variables, the following descriptive statistics

were computed: number of observations, mean, standard deviation, median, 25% and 75% quartile, minimum and maximum. Categorical variables were presented with absolute and relative frequencies within the single categories. If there were any missing data for categorical variables these were not excluded from analysis but displayed as a separate category with absolute and relative frequencies, too.

All analyses were performed with the full analysis set (FAS 1). The FAS 1 includes all primary study cohort patients (N=152) with existing informed consent form, fulfilling the inclusion criteria and not presenting with exclusion criteria documented in the eCRF.

Time to event analyses including overall survival (OS) were estimated using the Kaplan-Meier method to present 25th, 50th (median), and 75th percentiles of the time-to-event data together with the corresponding 95% confidence interval (CI), as well as the number and percentage of events and censored observations.

As this was a NIS, a certain number of missing values was expected. No statistical methods were used to replace missing values. Handling of missing questionnaire data is described in the respective manual and scoring procedures (2001).

Statistical analysis of final study results was performed using SAS™ Version 9.4. of the SAS System for Windows. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Results:

This non-interventional study recruited patients from May 26, 2016 until June 24, 2019. This final analysis was performed with database cut at May 31, 2020 comprising 159 patients from 53 centers observed over a period of 48 months. The full analysis set of the *primary study cohort* comprised 152 patients, 102 (67.1%) women and 50 (32.9%) men aged between 42 and 88 years at date of progression on/after TKI therapy. The smoking status of most patients 48.0% (n=73) was non-smoker, 39.5% (n=60) were previous smokers and 2.6% (n=4) were current smokers; 15% of patients had unknown smoking status. Most of the patients were diagnosed with an adenocarcinoma (95.4%). ECOG performance status at inclusion was ECOG 0-1 for 96 patients (63.2% of patients) and ECOG 2-3 for 19 patients (12.5%). For 37 patients (24.3%) ECOG performance status was not evaluated.

Molecular testing details:

Data on molecular tests were evaluable for 152 patients. In total, 355 tests were documented, 166 of these were performed before (i.e. pre-index date) and 189 after (i.e. post-index date) date of progression on/after TKI. Testing at time of initial diagnosis of NSCLC was performed in 131 patients (86.2%). Of these, 40 (26.3%) tests included detection of T790M mutation.

At progression (1 week prior to 5 weeks after date of progression on/after first EGFR-TKI therapy) 85 patients (55.9%) were re-tested. Most of these re-tests included detection of T790M mutation (94.1%, 80 out of 85). In 44.1% of the patients (n=67), no re-testing was performed at date of progression on/after first TKI. (Note that for one patient multiple testing at the same as well as testing at several points in time were possible).

Testing and detection of T790M mutation

Before progression (until 1 week prior to date of progression on/after EGFR-TKI therapy) 30.9% of the patients (n=47 out of 152 pts) were tested for T790M mutation. Of these, 12 patients (7.9%) were found to be positive for this mutation. In 35 patients (23.0%) a T790M mutation was not detected.

At/after progression on/after TKI (1 week prior to date of progression on/after EGFR-TKI therapy to end of study) molecular testing was performed in 132 patients (86.8%). Testing of T790M mutation was performed in 128 patients (84.2%). Of these, 89 patients (58.6%) had a T790M mutation. In 39 patients (25.7%) a T790M mutation was not detected. At/after progression only 4 patients (out of 132 patients with documented tests) were not tested for T790M.

Sample types for molecular tests:

Most documented tests (pre- and post-index date) were performed using formalin-fixed paraffin-embedded tissue (FFPE), 113 patients (74.3%). Testing of blood (plasma) was done in 53 patients (34.9%), cytology samples, 19 patients (12.5%). Tissue types for molecular tests were mainly derived from bronchoscopy (68 patients, 44.7%), endobronchial ultrasound (21 patients, 13.8%) and/or core needle biopsy (13 patients, 8.6%).

The testing turnaround time and testing laboratory types for molecular testing post-index date were documented for 188 tests. Mean and median turnaround time was 16.9 days and 10 days, respectively.

Treatment details:

For 149 patients (98%) a treatment following the progression on/after TKI therapy was documented. In the first line of treatment after progression on/after TKI therapy the substance most frequently administered was osimertinib (71 patients, 46.7%). Afatinib and gefitinib were given to 16 (10.5%) and 8 (5.3%) patients, respectively.

A second line of treatment following the progression on/after TKI treatment was documented for 88 patients (57.9% of all recruited patients in the primary cohort). In this line, a diverse range of treatments was used with osimertinib being the most commonly used substance (18 patients, 11.8%).

Overall, 106 (69.7%) patients were treated with osimertinib. In 88 of these patients (57.9%) T790M mutation was detected at any point of time. 7 (4.6%) patients were tested positive for T790M but were not treated with osimertinib.

Time to initiation of new therapy:

Median time to initiation of a new therapy (defined as the time from first start date of current therapy substances to first start date of subsequent therapy substances for all therapies that have a subsequent therapy)) was 7.9 months in 1st subsequent treatment, 4.8 months in 2nd subsequent treatment, 4.7 months in 3rd subsequent treatment and 7.0 months in 4th subsequent treatment after progression on/after TKI therapy, respectively, independently of used drug. The relative high proportion of missing data should be considered when interpreting data. Data on treatment patterns (time to initiation of next therapy, duration) in 1st/2nd/...subsequent treatment line after progression on/after TKI therapy should not be generalized or compared with data on second-/third/....-line treatment from other data sources since the number of prior lines of treatment was not specified in PANORAMA.

(CNS) metastases at diagnosis und at date of progression on/after TKI therapy:

At initial diagnosis of NSCLC, metastases in the central nervous system (CNS) were present in 33 patients (overall CNS metastases rate: 21.7%). No CNS metastases were found in 113 patients (74.3%). For 6 patients (3.9%) CNS metastases was documented to be unknown.
Rate of brain metastases was 17.8% (n=27). Leptomeningeal metastatses were found in 1 patient (0.7%), for 5 patients (3.3%) the location of CNS metastasis was documented to be unknown.

At date of progression on/after TKI therapy, overall CNS metastases was 23.0% (35 patients), the rate of brain metastases was 20.4% (31 patients). Existence of CNS metastases was unknown in 4 patients.

Health related quality of life (EORTC QLQ-C30 and LC13):

Interpretation of data on HRQoL is limited, because the total number of the returned questionnaires during follow-up was too low and will therefore not be reported.

Conclusion:

The non-interventional study PANORAMA gave an insight into molecular testing patterns and treatment in patients with EGFR-positive locally advanced or metastatic NSCLC who had progressed on/after TKI therapy. Patient characteristics were comparable to other studies: The majority of patients with EGFR-mutation were female, non-smokers and had adenocarcinoma. Next generation sequencing (NGS) was used more often than Sanger sequencing or other platforms, and while the majority of tests was performed on formalin-fixed paraffin-embedded tissue, about a third of the patients had tests based on blood samples. Despite the recommendations of European guidelines, not all patients were re-tested after progression on/after TKI therapy. If patients were tested, most of these tests included screening for T790M mutation. As expected, EGFR mutation status most often showed deletions in exon 19 and L858R mutation on exon 21. T790M mutations were detected at rather unexpectedly high frequencies (58.6% of all patients tested for T790M at/after progression). Osimertinib was the substance most frequently administered in the first line of treatment after progression on/after TKI therapy. Generalizability of the results might be limited by the study design (retrospective documentation of data prior to progression) and results indicate that the T790M test rate, percentage of T790M mutations and frequency of treatment with osimertinib might be overestimated due to selection bias.

Publications:

There are no full publications at the time of completion of this report.