1 Synopsis

1.1 General information about the study

Sponsor: AstraZeneca

Investigational Product: N/A

Type of study: observational, retrospective

Study title: Real-world Treatment Patterns, Clinical Outcomes and EGFR/T790M Testing Practices in EGFR-Mutated Advanced Non-SmalL CEll Lung Cancer Patients Receiving First-Line EGFR TKI Therapy (REFLECT)

[redacted]

[redacted]

[redacted]

Study dates: First Data collected (First Subject In): 07-May-2019
Last Data collected (Last Subject In): 31-Dec-2019

Report date: 21-Dec-2020

Synopsis

General information about the study

Introduction

Background

Non–small cell lung cancer (NSCLC) is the most frequently diagnosed cancer globally, with an estimated 1.8 million new cases worldwide in the year 2012. Until recently, NSCLC was treated as a single disease with predetermined treatment strategies based on general clinical criteria such as histology (adenocarcinoma versus squamous cell carcinoma), disease stage, tumor localization, and patient performance status. Median progression-free survival is usually 4 to 6 months for advanced stage patients receiving platinum doublet chemotherapy as first-line treatment, and 2 to 3 months for single-agent chemotherapy as second-line treatment. Median overall survival (OS) with these standard treatments is approximately 1 year.

Spurred by technological advances in recent years leading to an increased understanding of the molecular heterogeneity that drives oncogenesis in cancer cell survival and proliferation, NSCLC is increasingly classified by the presence of specific oncogenic mutations. Epidermal growth factor receptor (EGFR) mutation was the first oncogenic driver discovered in NSCLC and is prevalent in 10%-15% of lung cancer cases in Western countries. In this population, first-line treatment in the locally advanced/metastatic setting with the EGFR tyrosine kinase inhibitors (EGFR TKIs) erlotinib, gefitinib, or afatinib is recommended. Common alterations of EGFR mutations are exon 19 deletions and the L858R point mutation in exon 21, covering more than 90% of all mutations, which are sensitive to EGFR TKI therapy; other EGFR mutations, including the T790M mutation on exon 20, represent less than 10% of all mutations and are associated with drug resistance.

While EGFR TKIs remain the preferred first-line treatment for most advanced NSCLC patients with EGFR mutation, treatment after progression (i.e., second-line and beyond) is less well defined. There are several options currently available for treatment beyond progression in EGFR-mutated NSCLC, particularly for patients with EGFR alterations with known resistance to current therapies.

Rationale

The T790M mutation of the EGFR gene is the most common mechanism underlying resistance to first- or second-generation EGFR TKIs in patients with EGFR-mutated NSCLC. Osimertinib, a third-generation EGFR TKI, which has shown robust efficacy in patients with T790M-mutated advanced or metastatic NSCLC and resistance to prior EGFR TKI therapy, was EMA approved for use in NSCLC patients with a T790M mutation in February 2016. Later, in June 2018, additional EMA approval was received for use of osimertinib as first-line treatment for advanced/metastatic NSCLC cases with most common EGFR mutations. The approvals to use of osimertinib in first-line treatment in Switzerland and Israel were received in October 2018, and January 2019, respectively. All these approvals are based on the AURA3 and FLAURA trials.

To augment published data from these and other ongoing clinical studies, and to facilitate future evidence evaluations for osimertinib and other next-generation EGFR TKIs across Europe, this study seeks to obtain real-world data on prevailing treatment patterns, clinical outcomes, and EGFR / T790M testing practices in patients with EGFR-mutated NSCLC treated with a first-line regimen containing a currently approved first- or second-generation EGFR TKI (i.e., erlotinib, gefitinib, or afatinib). Eight countries from Western and Eastern Europe as well as Israel participated in this study.

Study objectives

The purpose of this study was to describe the real-world treatment patterns, clinical outcomes, and EGFR / T790M testing practices in EGFR-mutated advanced NSCLC patients receiving first-line EGFR TKI therapy.

No formal study hypothesis was tested.

Primary objective(s)

1. To describe the type of first or second generation EGFR TKI used in first-line therapy.
2. To evaluate the proportion of patients progressing on first line EGFR TKI therapy and describe the progression free survival.
3. Among patients progressing on first-line EGFR TKI therapy: to describe the proportion of patients receiving second line therapy and type of second-line therapy [e.g., chemotherapy, osimertinib, other EGFR TKI, immuno-oncology therapy (I/O) or other therapy].

Secondary objective(s)

1. To describe the patients' demographic and baseline disease characteristics.
2. To explore the type of sample & test used to determine the EGFR mutation (e.g., primary or secondary tumor, tissue biopsy / cytology or blood sample, type of test).

3. To describe the proportion of patients with brain metastases (BM) among metastatic patients (proportion of patients with BM since diagnostic of metastatic disease and proportion of patients with BM developed during treatment) and to describe the overall survival (OS) expectation in the group of patients with BM, from BM diagnosis.
4. To describe the proportion of patients with leptomeningeal disease (LM) among metastatic patients (proportion of patients with LM since diagnostic of metastatic disease and proportion of patients with LM developed during treatment) and to describe the overall survival expectation in the group of patients with LM disease, from LM diagnosis.
5. To explore the proportion of patients where the first-line therapy with first- or second-generation EGFR TKI is associated with any other systemic therapy, including the type of systemic therapy.
6. Among patients progressing on first-line EGFR TKI therapy and tested for T790M mutation: to describe the proportion of patients receiving second-line therapy and type of second line therapy received (e.g., chemotherapy, osimertinib, other EGFR TKI, I/O, or other therapy).
7. Among patients progressing on first-line EGFR TKI therapy: to describe the proportion of patients tested for T790M mutation and the proportion of patients with positive mutation, as well as the type of sample & test used to determine the mutational status (e.g., tissue biopsy / cytology or blood sample, type of test).
8. Among patients progressing on first-line EGFR TKI therapy and not tested for T790M mutation: to describe the proportion of patients receiving second line therapy and type of second line therapy received (e.g., chemotherapy, osimertinib, other EGFR TKI, I/O, or other therapy).
9. To describe how the proportion of patients receiving second line therapy differs between patients tested for T790M mutation and patients not tested for T790M mutations.
10. To describe the proportion of patients receiving third- or later-line therapy and type of this therapy and to explore whether the proportion receiving third- or later-line therapies vary by the second-line therapy category (chemotherapy, osimertinib, other EGFR TKI, I/O therapy, or other therapy) received.
11. To explore the overall survival expectation for these patients from first diagnosis of locally advanced or metastatic disease and from start of first line EGFR TKI therapy.
12. To explore the incidence of other mutations, in case additional molecular testing was performed either at the time of initial EGFR testing or at the time of T790M testing.

Study design

General description

This was a retrospective, non-interventional, multinational, multi-center medical record review to describe the treatment patterns, clinical outcomes, and EGFR / T790M testing practices in EGFR-mutated advanced NSCLC patients receiving first-line EGFR TKI therapy. The study was conducted in: Austria, Bulgaria, Greece, Israel, Poland, Romania, Slovenia, and Switzerland.

The regional and local study teams identified suitable oncology centers to ensure an adequate sample of eligible patients at study and country level. Participating physicians were experienced medical oncologists and pulmonologists responsible for making treatment decisions for NSCLC patients under their care and with a case-load of at least 4 EGFR-mutated NSCLC patients in the past year. It was anticipated that each participating Investigator would contribute with 5 to 20 patient records to the study. The initial quota per Investigator was set to 5 patient records in order to ensure a representative sample at country level. The quota was allowed to increase if needed to meet the country target.

Patients were identified in the chronological order of starting the first-line EGFR TKI therapy within the study entry window (e.g., starting with Jan 1, 2015). In case of meeting all study inclusion criteria, patients were enrolled in the electronic platform containing the case report forms in a consecutive manner.. For each patient enrolled in the study, data were collected from their initial diagnosis of NSCLC through death or the last medical record available at the moment of inclusion in the study.

Study population

Data were collected from a cohort of 896 patients meeting eligibility criteria across Europe and Israel. [redacted]

Inclusion / Exclusion criteria

Inclusion criteria

1. Confirmed diagnosis of locally advanced unresectable or metastatic NSCLC,
2. Aged at least 18 years at first diagnosis of locally advanced/metastatic NSCLC,

3. Lab-confirmed EGFR mutation,
4. Received a first- or second-generation EGFR TKI as first-line treatment for advanced/metastatic disease,
5. First-line EGFR TKI (afatinib, gefitinib, erlotinib) initiated between January 1, 2015 and June 30, 2018,
6. Patients alive or deceased at the time of medical record review.

The study entry window for first-line EGFR TKI initiations between January 1, 2015 and June 30, 2018 was chosen to balance the opportunity for maximal follow-up and low censoring on survival with the capture of recently prevailing patterns of care.

Exclusion criteria

1. Patients enrolled at any time in an interventional clinical trial for an experimental treatment related to EGFR-mutated NSCLC,
2. Patients receiving any systemic therapy for locally advanced or metastatic NSCLC prior to first-line EGFR TKI treatment in the locally advanced/metastatic setting,
3. Missing or unknown data on any of the following key study dates:
    - Date of initial NSCLC diagnosis,
    - Date of first diagnosis of or progression to advanced/metastatic NSCLC,
    - Date of first-line EGFR TKI initiation for advanced/metastatic disease,
    - Date of death or last available follow-up.

[redacted]

Statistical Methods

All statistical analyses were descriptive. No formal statistical comparisons between groups were planned. It was estimated that a sample size of between 700 and 820 was required to provide sufficient precision for estimating median progression free survival, the primary outcome, based on the assumption of 55% data maturity.

Median progression free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier estimator. All results were stratified by country (not reported here). For the stratified OS analysis, the number of events had to be greater than 20 and the level of maturity greater than 50%. For all measures of OS, patients known to be alive at last date of available follow-up were censored.

Results

The number of patients involved in the study was 899, hence the Full Analysis Set (FAS) includes 899 subjects. There were 3 subjects who did not fulfill the inclusion/exclusion criteria. The Per-Protocol Population (PP) included 896 subjects. The calculations are based on the Per-Protocol Population.

There were 49 sites involved in the study from 8 participating countries. The primary practice setting was Regional/National Cancer Centre for 17 sites, Teaching/Academic University hospital for 18 sites, General (non-teaching) Hospital for 6 sites and Private Hospital or Clinic for 8 sites.

Primary objectives

1. **Type of first EGFR TKI therapy.** The type of first EGFR TKI therapy was afatinib for 407 subjects (45.4%), erlotinib for 245 subjects (27.3%) and gfor 244 subjects (27.2%).

2. **Progression on first line EGFR TKI therapy.** The first-line EGFR TKI was stopped for 765 subjects (85.4%), while it was ongoing at the end of the study for 131 subjects (14.6%). The four type of progression events were imagistic progression with 461 cases (51.5%), clinical progression with 113 cases (12.6%), death with 86 cases (9.6%) and start of new therapy line without progression with 63 cases (7.0%). The median progression free survival on first line EGFR TKI therapy was 13.0 months with 95% confidence interval (CI) of 12.3, 14.1 months. (Kaplan-Meier estimator has been used throughout the report.)

3. **Second line therapy characteristics.** The number of patients who started a second-line therapy is 515. The median time between the start of EGFR TKI 1L and the start of 2L was 13.11 months. [redacted] The second line systemic treatments included (multiple therapies could be selected for a patient): chemotherapy with 163 cases (31.7%), osimertinib with 308 cases (59.8%), Targeted therapy with 34 cases (6.6%), immuno-oncological therapy with 23 cases (4.5%) and other therapy with 10 cases (1.9%). The second line therapy was ongoing for 120 subjects (23.3%) at the end of the study. The reasons for discontinuation of the second-line therapy included: imagistic progression with 171 cases (33.2%), clinical progression with 65 cases (12.6%), death with 87 cases (16.9%), other reason with 59 cases (11.5%) and unknown with 13 cases (2.5%).

Secondary objectives

1. **Demographic and baseline disease characteristics.** The average age of the subjects at first diagnosis of locally advanced/metastatic NSCLC is 67.03 years. [redacted]. The number of the female subjects is 574 (64.1%), while the male subjects' number is 322 (35.9%). There were 2-5 years between initial NSCLC diagnosis and medical review for 676 subjects (75.4%). Tumor histology at initial diagnosis was

adenocarcinoma for 856 subjects (95.5%). Stage at initial diagnosis was *metastatic* for 713 subjects (79.6%). The smoking status at initial diagnosis was *never smoker* for 460 subjects (51.3%). ECOG at initial diagnosis was *0* for 291 subjects (32.5%) and *1* for 332 subjects (37.1%). It was unknown for 183 subjects (20.4%). The median time between initial NSCLC diagnosis and first diagnose of locally advanced unresectable / metastatic NSCLC was 0.00 months [redacted]

2. **EGFR mutation characteristics.** The median time between initial NSCLC diagnosis and EGFR testing was 0.49 months [redacted] The type of identified EGFR mutation was Exon 19 deletion for 488 subjects (54.5%), L858R mutation for 280 subjects (31.3%) and Other EGFR mutation for 128 subjects (14.3%).

3. **Patients with brain metastases.** [redacted] there were 198 subjects (22.1%) who had BM at start of first-line EGFR TKI therapy [redacted]

4. **Patients with leptomeningeal disease.** [redacted]

[redacted]

5. **Other systemic treatment(s) in combination with first-line EGFR TKI.** In combination with the first-line EGFR TKI the following systemic treatments were used: chemotherapy for 2 subjects (0.2%), targeted therapy for 12 subjects (1.3%), immuno-oncological therapy for 15 subjects (1.7%) and other therapy for 32 subjects (3.6%).

6. **T790M mutation testing among patients progressing on first-line EGFR TKI therapy.** There were 723 patients who progressed on first-line EGFR TKI therapy. Among patients progressing on first-line EGFR TKI therapy, 513 subjects (71.0%) were tested for T790M mutation any time, while 210 subjects (29.0%) were not tested. The T790M test result was positive for 299 subjects (58.3%) and negative for 213 subjects (41.5%). [redacted] The type of specimen was tissue biopsy for 109 subjects (21.2%), cytology specimen for 31 subjects (6.0%) and liquid biopsy for 370 subjects (72.1%). Among the 299 patients with positive T790M test result, 283 (94.6%) received osimertinib in line 2/3/4/5.

7. **Second-line therapy characteristics for patients progressing on first-line EGFR TKI therapy with T790M testing.** Among patients progressing on first-line EGFR TKI therapy, 513 were tested for T790M mutation any time. Among them 443 subjects (86.4%) were treated with second-line therapy. The second line systemic treatments include (multiple therapies could be selected for a patient): chemotherapy with 118 cases (26.6%), osimertinib with 296 cases (66.8%), targeted therapy with 22 cases (5.0%), immuno-oncological therapy with 16 cases (3.6%) and other therapy with 6 cases (1.4%). [redacted]

8. **Second-line therapy characteristics for patients progressing on first-line EGFR TKI therapy without T790M testing.** Among patients progressing on first-line EGFR TKI therapy, 210 were *not* tested for T790M mutation any time. [redacted]

[redacted]

9. **Second line therapy and T790M mutation testing.** [redacted]

10. **Third and later line therapy characteristics.** The number of patients who started a third-line therapy is 183. The third line systemic treatments include (multiple therapies could be selected for a patient): Chemotherapy with 113 cases (61.7%), Osimertinib with 30 cases (16.4%), Targeted therapy with 26 cases (14.2%), Immuno-oncological therapy with 28 cases (15.3%) and Other therapy with 8 cases (4.4%). The number of patients who started a fourth-line therapy was 55. [redacted] The number of patients who started a fifth-line therapy was 20. [redacted]

11. **Overall survival.** Among the patients there were 542 (60.5%) deaths, while there were 354 (39.5%) censored cases (patients who were alive according to last vital status). [redacted] The median time to death from start of first line EGFR TKI therapy was 26.2 months with 95% confidence interval (CI) of 23.6, 28.4 months. [redacted]

12. **Incidence of other mutations.** [redacted]

SIGNATURES

ASTRAZENECA SIGNATURE(S)

Real-world Treatment Patterns, Clinical Outcomes and EGFR/T790M Testing Practices in EGFR-Mutated Advanced Non-SmalL CEll Lung Cancer Patients Receiving First-Line EGFR TKI Therapy (REFLECT)

This Observational Study Synopsis has been subjected to an internal AstraZeneca review. I agree to the terms of this Study synopsis.

AstraZeneca Representative

DocuSigned by:
Rene G. Ott
E5EEEFA5C3784D0...

Head of Medical Information

Rene Ott

Head of Medical Information, Oncology

Rene.ott@astrazeneca.com

Date Dezember 22, 2020

Day/ Month/ Year