AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Tagrisso Tablets
ACTIVE INGREDIENT: Osimertinib mesilate tablets

Study No: D5160C00025
NCT02756039

Developmental Phase: Post-marketing
Study Completion Date: August 2018
Date of Report: August 2019

OBJECTIVES:

Clinical Experience Investigation (CEI) was conducted in Japan to confirm following to characterise safety and efficacy of Osimertinib as the second- or later-lines treatment of patients with EGFR T790M mutation-positive non-small cell lung cancer who have progressed on EGFR-TKIs in actual clinical use.

- Frequency of Adverse Drug Reactions (ADRs)* in actual clinical use
- Seek factors which may affect safety and efficacy of the product (especially for characteristics of Interstitial lung disease (ILD) related events and to analyse risk factors of ILD-related events)
- Collect information of ADRs not expected from "Precautions for Use" of the Japanese Prescribing Information (JPI)

*: Adverse events whose causality to Osimertinib could not be denied by attending physicians or AstraZeneca

METHODS:

Observational Study

RESULTS:

Results were based on all data on patients enrolled to CEI and treated with Osimertinib that were locked between 28 March 2016 (Osimertinib marketing/manufacturing approval date in Japan) and 31 August 2018 (the data lock date of the report). In total, all data on 3629 patients were included in CEI.

In these 3629 patients, the number of patients included in the safety analysis set was 3578 patients. In these 3578 patients, the number of patients included in the efficacy analysis set was 3563 patients.

■ **Development of ADR/infection events**

In the 3578 patients of the safety analysis set, with the median observation period of 343 days (range: 1-764), ADRs were reported in 58.1% (2079 patients) of patients (4255 events).

Common ADRs (frequencies 5% or higher) were diarrhoea 10.9% (390 patients), paronychia 10.3% (370 patients), rash 8.5% (304 patients), and platelet count decreased 6.2% (221 patients), decreased appetite 5.8% (207 patients), and interstitial lung disease 5.5% (197 patients).

ADRs of CTCAE Grade 3 or higher and with frequency 0.5% or higher were interstitial lung disease 2.4% (85 patients), neutrophil count decreased 1.2% (43 patients), decreased appetite 0.7% (24 patients), diarrhoea 0.7% (25 patients), platelet count decreased 0.7% (24 patients), anaemia 0.6% (21 patients), and white blood cell count decreased 0.6% (23 patients).

In the 2079 patients with ADR, the fatal outcome was reported in 52 patients that details were: interstitial lung disease in 22 patients; lung disorder in 4 patients; cardiac failure in 3 patients; pulmonary toxicity, pulmonary embolism, and death each in 2 patients; pneumonia, septic shock, subcutaneous abscess, pneumonia bacterial, B-cell lymphoma, cerebral haemorrhage, acute myocardial infarction, cardiac failure chronic, cardiac failure acute, cardio-respiratory arrest, ventricular hypokinesia, acute respiratory distress syndrome, pneumonia aspiration, pneumothorax, pulmonary artery thrombosis, gastrointestinal perforation, pancreatitis necrotising, hepatic function abnormal, renal failure, sudden death, and spinal compression fracture each in one patient.
All events were preferred terms (PTs) per MedDRA/J 21.0.

■ **ADRs of ILD-related events**

➢ **ILD-related events (Investigator assessment)**

In the 3578 patients of the safety analysis set, ILD-related events were reported in 6.8% (245/3578) of the patients. The fatal outcome was reported in 29 of 245 patients.
ILD-related events (investigator assessment) were grouped terms of investigator-reported AEs consisting of 12 PTs (not including lab/ECG abnormalities which were not reported by investigator).

➢ **ILD-related events (Committee assessment)**

Based on the primary and sensitivity risk factor analyses of ILD development for 3578 patients in the safety analysis set (including 231 patients with ILD rated by the ILD expert committee Japan) using the multivariate logistic regression models, prior treatment of nivolumab and history/concurrence of ILD were common factors where the point estimate of adjusted odds ratio being > 2 and the lower limit of asymptotic 95% confidence interval being > 1, suggesting that they are potential risk factors for ILD development.

Regarding patients with prior treatment with nivolumab, the possibility of risk of ILD incidence which are driven by either the ongoing treatment with Osimertinib or post-

discontinuation from prior treatment with nivolumab needs to be noted in an ongoing basis.

ILD-related events (committee assessment) were grouped terms of investigator-reported AEs consisting of MedDRA ILD SMQ or lung disorder (not including lab/ECG abnormalities which were not reported by investigator).

■ ADRs other than ILD

Following ADRs of concern which is priority surveillance items as per Japanese risk management plan of Osimertinib other than ILD were investigated; QT interval prolonged, liver disorder, haematotoxicity, cardiac disorder (excluding QT interval prolonged), infection, thromboembolism, corneal disorder, and diarrhoea/skin disorder/paronychia of Grade 3 or higher. The number of patients and frequencies of these events were: QT interval prolonged in 45 patients (1.3%), liver disorder in 212 patients (5.9%), haematotoxicity in 409 patients (11.4%), cardiac disorder (excluding QT interval prolonged) in 101 patients (2.8%), infection in 79 patients (2.2%), thromboembolism in 45 patients (1.3%), corneal disorder in 20 patients (0.6%), diarrhoea of Grade 3 or higher in 25 patients (0.7%), skin disorder of Grade 3 or higher in 26 patients (0.7%), and paronychia of Grade 3 or higher in 16 patients (0.4%).

■ Efficacy

The best overall response was assessed in 3563 patients of the efficacy analysis set according to “New response evaluation criteria in solid tumours (RECIST) version 1.1” (evaluated by attending physicians).

- Antitumour effect

  The best overall response included “complete response” 119 patients, and “partial response” 2373 patients. The overall response rate (complete response + partial response) was 69.9% (2492/3563 patients, 95% CI: 68.4-71.4%).

- Disease control

  The disease control rate (complete response + partial response + stable disease) was 86.7% (3090/3563 patients, 95% CI: 85.6-87.8%).

■ Summary

No new findings that would affect the risk-benefit balance assessment of Osimertinib have been found in this report.