

Supplementary Material. Inclusion and exclusion criteria

Inclusion criteria

For inclusion in this study, subjects were required to fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures
2. Age > 18 years
3. Presence of locally advanced or metastatic non-small cell lung cancer, not amenable to curative surgery or radiotherapy, with or without pathologic diagnosis
4. No prior exposure to epidermal growth factor receptor tyrosine kinase inhibitors (multiple lines of prior cytotoxic chemotherapy are permitted.)
5. Activating *EGFR* mutation (G719X, exon 19 deletion, L858R, L861Q) detected from circulating tumor DNA, either by PANA Mutyper or Cobas *EGFR* mutation tests
6. Activating *EGFR* mutation (G719X, exon 19 deletion, L858R, L861Q) detected from tumor tissue or cytology specimen
7. World Health Organization (WHO) performance status of 0-2
8. A life expectancy \geq 12 weeks
9. Females must be taking adequate contraceptive measures, must not be breast feeding, and must have a negative pregnancy test result prior to the start of dosing, if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening: (1) post-menopausal, defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments, (2) women under 50 years of age were considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution;

*(3) documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

10. Male patients should be willing to use barrier contraception (see Restrictions, Section 3.5).
11. Willingness and ability to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations, including follow-up
12. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥ 15 mm), with computed tomography

Exclusion criteria

Subjects did not enter the study if any of the following exclusion criteria were fulfilled:

1. Any unresolved toxicities from prior therapy, greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 at the time of study treatment initiation, with the exception of alopecia and grade 2, prior platinum-therapy-related neuropathy
2. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion make it undesirable for the patient to participate in the trial or would jeopardize compliance with the protocol, or active infections, including hepatitis B, hepatitis C, or human immunodeficiency virus (Screening for chronic conditions was not required.)
3. Symptomatic central nervous system metastases that are neurologically unstable

4. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD

5. Inadequate bone marrow reserves or organ functions, as demonstrated by any of the following laboratory values:

Absolute neutrophil count $< 1.5 \times 10^9/L$

Platelet count $< 100 \times 10^9/L$

Hemoglobin levels $< 90 \text{ g/L}$

Alanine aminotransferase levels > 2.5 times the upper limit of normal (ULN), if no demonstrable liver metastases, or > 5 times the ULN in the presence of liver metastases

Aspartate aminotransferase levels > 2.5 times the ULN, if no demonstrable liver metastases, or > 5 times the ULN in the presence of liver metastases

Total bilirubin levels > 1.5 times the ULN, if no liver metastases, or > 3 times the ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases

Creatinine levels > 1.5 times the ULN, concurrent with creatinine clearance < 50 mL/min (measured or calculated by the Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine levels were > 1.5 times the ULN

6. Any of the following cardiac criteria:

a. Mean resting corrected QT interval (QTc using Fredericia's formula) > 470 msec

b. Any clinically important abnormalities in rhythm, conduction, or morphology identified in a resting electrocardiography (e.g., complete left bundle branch block, third-degree heart block, second-degree heart block)

- c. Any factors that increase the risk of QTc prolongation or arrhythmic events, such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, unexplained sudden death under 40 years of age in first-degree relatives, or any concomitant medication known to prolong the QT interval
7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of Osimertinib.
8. History of hypersensitivity to osimertinib (or drugs with a similar chemical structure or class to osimertinib) or any excipients of these agents
9. Males and females of reproductive potential who are not using an effective method of birth control and females who are pregnant, breastfeeding, or have a positive (urine or serum) pregnancy test result prior to study entry
10. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements
11. Previous allogeneic bone marrow transplantation
12. Non-leukocyte-depleted whole blood transfusion within 120 days of the date of the genetic sample collection