

Supplementary Material

1. Inclusion and exclusion criteria

1) Inclusion criteria

For inclusion in this study, subjects must fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedure.
2. Patients (male/female) must be ≥ 18 years of age.
3. Locally advanced or metastatic non-small cell lung cancer that is not amenable to curative surgery or radiotherapy, with or without pathologic diagnosis.
4. Progression after prior exposure to gefitinib, erlotinib, afatinib, or dacomitinib. Multiple lines of prior cytotoxic chemotherapy are permitted, and there is no specified order of treatment.
5. Patients must fulfil one of the following:
 - 5.1) Activating *EGFR* mutation (G719X, exon 19 deletion, L858R, L861Q) from tumor tissue, cytology, or circulating tumor DNA,
 - 5.2) Must have experienced clinical benefit from prior EGFR-TKI, according to the Jackman criteria, followed by systemic objective progression (RECIST) while on continuous treatment with EGFR-TKI.
6. T790M mutation detected from circulating tumor DNA, either by PANA MutyperTM or CobasTM *EGFR* mutation test version 2.
7. World Health Organization (WHO) performance status of 0-2.
8. Patients must have a life expectancy ≥ 12 weeks.
9. Women should be using adequate contraceptive measures, should not be breastfeeding, and must have a negative pregnancy test 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:

*Post-menopausal, defined as age greater than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.

*Women under 50 years of age would be considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments, and if they had luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for the respective institution.

*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.
11. The patient is willing and able to comply with the protocol for the duration of the study, including undergoing treatment, scheduled visits, and follow-up examinations.
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 (CT).

2) Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Previous treatment with osimertinib, or other third generation EGFR-TKI.
2. Treatment with an investigational drug within five half-lives of the compound.
3. Patients currently receiving (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors of CYP3A4 (at least 1 week prior) and potent inducers of CYP3A4 (at least 3 weeks prior).

All patients must try to avoid concomitant use of any medications, herbal supplements, and/or ingestion of foods with known inducer/inhibitory effects on CYP3A4.

4. 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.
5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the investigator's opinion makes 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, and human immunodeficiency virus (HIV). Screening for chronic conditions is not required.
6. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable.
7. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis requiring steroid treatment, or any evidence of clinically active ILD.
8. 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 $< 90 \text{ g/L}$.

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

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

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

Creatinine > 1.5 times ULN concurrent with creatinine clearance < 50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is > 1.5 times ULN.

9. 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 of resting ECG (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 risk of 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.
10. 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.
11. History of hypersensitivity to osimertinib (or drugs with a similar chemical structure or class to osimertinib) or any excipients of these agents.
12. Men and women of reproductive potential who are not using an effective method of birth control, and women who are pregnant, breastfeeding, or have a positive (urine or serum) pregnancy test prior to study entry.
13. 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.
14. Previous allogeneic bone marrow transplantation.

15. Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.