ORIGINAL ARTICLE

# Cost-Effectiveness of Osimertinib for *EGFR* Mutation–Positive Non–Small Cell Lung Cancer after Progression following First-Line EGFR TKI Therapy

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**ABSTRACT**

**Objective:** The aim of this study was to investigate the cost-effectiveness of osimertinib for the treatment of advanced NSCLC with an *EGFR* T790M mutation after the failure of first-line EGFR tyrosine kinase inhibitor (TKI) therapy.

**Methods:** A mathematical model was established by combining a decision tree and the Markov approach to project the cost-effectiveness of osimertinib versus standard chemotherapy for the treatment of patients who harbor an *EGFR* T790M mutation and have disease progression after first-line EGFR TKI therapy with or without metastases to the central nervous system. The clinical and outcome data were derived from randomized clinical trials and published reports. The health outcome data included quality-adjusted life-years (QALY). The cost data were estimated from the perspectives of the payer in the United States and the health care system in the People's Republic of China. All costs and incremental cost-effectiveness ratios (ICERs) were presented in 2017 U.S. dollars. Sensitivity and scenario analyses with three different settings of T790M mutation testing were performed.

**Results:** Compared with chemotherapy, molecular testing in plasma and tissue followed by osimertinib treatment yielded an additional 0.359 and 0.313 QALYs in the entire U.S. population and the population of those with central nervous system metastases and an *EGFR* T790M mutation. For these populations, the incremental costs were $83,515 and $74,924 per patient, respectively, and the ICERs were $232,895 and $239,274 per QALY, respectively. For the entire Chinese population and the Chinese population with central nervous system metastases, the ICERs were $48,081 and $53,244 per QALY, respectively. For those with a known T790M mutation, the ICERs of osimertinib over chemotherapy also exceeded the willingness-to-pay threshold. The most influential parameter was the price of osimertinib.

**Conclusion:** Osimertinib treatment for T790M mutation NSCLC is unlikely to be cost-effective from the perspectives of the United States and the People's Republic of China. If the price of osimertinib could be decreased, the economic outcome might become favorable.



*Keywords:* Non-small-cell lung cancer; T790M mutation; Cost-effectiveness; Osimertinib

## Introduction

The Global Burden of Disease 2015 Study revealed that lung cancer is the leading cause of non-communicable disease burden.[1] Because of its poor outcomes, lung cancer was the most frequent cause of cancer death among all cases globally and among all sociodemographic index quintiles, except in regions with a low sociodemographic index group.[2] The disability-

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adjusted life-years associated with tracheal, bronchus, and lung cancer were 36.4 million in 2015, of which premature mortality accounted for 99% and years lived with disability accounted for 1%. Approximately 85% to 90% of lung cancers are NSCLC, and 10% to 15% of white patients and 30% to 50% of Asian patients carry *EGFR* mutations that play a key role in carcinogenesis.

First- and second-generation EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and afatinib have been recommended for the first-line of treatment of advanced *EGFR* mutation–positive NSCLC because of their significant superiority over standard chemotherapy in prolonging survival.[3] However, resistance against EGFR TKIs develops in patients, with a median progression-free survival (PFS) of 9 to 13 months and with 50% to 60% contributing to the emergence of an *EGFR* T790M gatekeeper mutation.[4] Osimertinib is a third-generation EGFR TKI designed to inhibit the growth of *EGFR* T790M–positive tumors; it has been approved for the treatment of patients with advanced NSCLC with *EGFR* T790M mutations in the United States and numerous other countries.[4] According to the pivotal phase III AURA3 trial, osimertinib treatment significantly prolonged PFS compared with platinum-pemetrexed therapy in patients with T790M-positive advanced NSCLC who experienced disease progression after EGFR TKI therapy (10.1 months versus 4.4 months; hazard ratio [HR] = 0.30, 95% confidence interval [CI]: 0.23–0.41, $p < 0.001$). For patients with central nervous system (CNS) metastases, osimertinib exhibits a favorable PFS benefit (8.5 months versus 4.2 months; HR = 0.32; 95% CI, 0.21–0.49).[5]

The clinical benefits of osimertinib treatment in patients for whom first-line EGFR TKI therapy has failed has inspired many oncologists and patients. However, because of the widespread use of osimertinib, the considerable increase in financial burden has become a topic of concern for decision makers in developed and developing regions because patients treated with TKIs are managed until disease progression or absence of tolerability. Economic evaluation of osimertinib has become an urgent need. To the best of our knowledge, the cost-effectiveness of osimertinib has not been assessed. The current analysis investigates the cost-effectiveness of osimertinib treatments in patients with advanced NSCLC and disease progression after first-line EGFR TKI therapy in the context of the United States and the People's Republic of China, which represent developed and developing countries, respectively.

## Methods

### Overview

A mathematical model was established by combining a decision tree and the Markov approach to measure the clinical and economic outcomes of osimertinib treatment in patients with *EGFR* T790M–positive advanced NSCLC after the failure of first-line therapy with first-generation EGFR TKIs. Because of the considerable impact of health resource consumption associated with mutation testing, the decision trees included the following three scenarios: (1) all patients undergo a blood sample screening to test the T790M mutation in plasma, and those with negative reports in plasma testing undergo a tissue biopsy to examine the T790M mutation status in their tissue; (2) all patients receive only T790M mutation testing in plasma and no further tissue testing for those with negative results in plasma; and (3) only patients with confirmed T790M mutation–positive NSCLC are included. Patients were considered to start either four-cycle pemetrexed plus cisplatin (PC) chemotherapy followed by pemetrexed maintenance therapy or osimertinib treatment after the T790M mutation–positive status was confirmed. A Markov model was established to reflect the disease course of advanced NSCLC, which included the following health states: PFS, progressed survival, and death. The Markov cycle length was 21 days, which is consistent with the schedule of PC chemotherapy,[5] and the time horizon was 10 years. During each Markov cycle, the model redistributes the hypothetical patients among the three health states according to the transition probabilities. The initial state is assumed to be progression-free, and death is the terminal state.

The following outcomes were examined: progression-free life-years (LYs), overall LYs, quality-adjusted life-years (QALYs) and cost. Cost and QALYs were discounted by 3% and 5% annually in the U.S. and Chinese contexts, respectively. The costs are shown as U.S. dollars. All costs have been adjusted to 2017 prices according to the local Consumer Price Index and are shown as US dollars (1 US dollar = 6.8 Chinese yuan renminbi). The incremental cost-effectiveness ratios (ICERs), which are presented as the cost per additional QALY gained, were also examined. As in previous analyses,[6–8] we used $100,000 and three times the per capita gross domestic product in the People's Republic of China in 2016 ($23,815) as the cost-effectiveness threshold in the U.S. and Chinese contexts, respectively. This economic analysis was based on a literature review and an experimental model and did not require approval from an institutional review board or ethics committee.

### Clinical Data

The clinical effectiveness data were obtained from the AURA3 trial.[5] On the basis of the goodness-of-fit examination measured by the $R^2$ statistic, the Weibull model $S(t) = exp(-\alpha t^{\beta})$ and log-logistic survival function