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Cost-effectiveness of Osimertinib in the First-Line Treatment of Patients With *EGFR*-Mutated Advanced Non–Small Cell Lung Cancer

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IMPORTANCE The survival of patients with advanced non–small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) gene mutations has improved substantially in the last decade with the development of targeted tyrosine kinase inhibitors (TKIs). Osimertinib, a third-generation TKI that is approved by the US Food and Drug Administration for the treatment of patients who develop *EGFR* T790M mutations, has recently shown improved clinical outcomes compared with gefitinib and erlotinib for treatment-naive patients.

OBJECTIVE The aim of this study was to assess the cost-effectiveness of osimertinib for the first-line treatment of patients with *EGFR*-mutated NSCLC.

DESIGN, SETTING, AND PARTICIPANTS For this cost-effectiveness analysis, we extracted individual patient data from the FLAURA randomized clinical trial and used findings of our earlier meta-analysis to develop a decision-analytic model and determine the cost-effectiveness of osimertinib (AZD9291) compared with first- and second-generation EGFR-TKIs over a 10-year time horizon. All direct costs were based on US and Brazilian payer perspectives.

MAIN OUTCOMES AND MEASURES The main outcome of this study was the incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life-year (QALY) gained by using osimertinib compared with first- or second-generation EGFR-TKIs in previously untreated *EGFR*-mutated NSCLC.

RESULTS In the base case using the data as reported in the FLAURA trial, the incremental QALY for osimertinib was 0.594 compared with the first- and second-generation EGFR-TKIs. In the United States, the osimertinib ICERs were $226 527 vs erlotinib, $231 123 vs gefitinib, and $219 874 vs afatinib. In Brazil, the ICERs were $162 329, $180 804, and $175 432, respectively. The overall survival (95% CI) reported in the FLAURA trial (hazard ratio, 0.63; 95% CI, 0.45-0.88) had the strongest association with the ICER (ranging from $84 342 to $859 771). Osimertinib price adjustments to the FLAURA trial data improved cost-effectiveness. For example, a discount of 10% on osimertinib acquisition cost was associated with a 20% decreased ICER compared with the base case ICER, and a discount of 20% on osimertinib acquisition cost was associated with a 40% decreased ICER compared with the base case ICER.

CONCLUSIONS AND RELEVANCE At current costs, by World Health Organization cost-effectiveness threshold criteria, osimertinib is not cost-effective for first-line therapy of *EGFR*-mutated NSCLC in either the United States or Brazil.

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Supplemental content

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Lung cancer remains the most common cancer and the leading cause of cancer deaths worldwide.[1] A substantial minority of patients with adenocarcinomas, who account for 70% to 85% of all non–small cell lung cancers (NSCLCs), harbor activating epidermal growth factor receptor (*EGFR*) mutations.[2] These patients are treated with first-line tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, or afatinib, which can lead to median progression-free survival (PFS) of 10 to 14 months.[3-5]

However, the vast majority of patients eventually develop resistance. One of the most common mechanisms of resistance is the development of secondary mutations such as the p.Thr790Met (T790M) point mutation, seen in more than half of patients.[6] Osimertinib is a potent irreversible EGFR-TKI that blocks both the common *EGFR*-activating mutations (exon 19 deletion or L858R) and the T790M mutation.[7] In the extension of AURA, a phase 2 study,[7] the efficacy of osimertinib was tested in T790M-positive patients after progression during treatment with first-generation TKIs. Median PFS was 12.3 months, and the duration of response was 15.2 months in responders.[7] Central nervous system lesion response rate at 64% also seemed better than what was achieved with previous-generation TKIs.[7] The osimertinib resistance mechanism is not completely known. Ou et al[8] performed next-generation sequencing in tumor samples from 99 osimertinib-resistant patients. They found *EGFR* C797 variants in 22% of patients, L792 mutations in 10% of patients, and a further 7% cases with L718 mutations.[8] Their data were compatible with in vitro findings of L792 and L718 mutations likely to cause osimertinib resistance.[8]

Recently, in the FLAURA trial,[9] osimertinib was compared with first-generation EGFR-TKIs in treatment-naive patients with advanced NSCLC and *EGFR* mutation.[9] Median PFS was superior with osimertinib (18.9 months vs 10.2 months with the first-generation EGFR-TKIs erlotinib and gefitinib). Based on these results, the National Comprehensive Cancer Network incorporated osimertinib as a first-line option in its guidelines.[10] In this study, we evaluate the cost-effectiveness of first-line treatment with osimertinib compared with gefitinib, erlotinib, and afatinib in the Brazilian and US settings.

Key Points

Question Is osimertinib, a third-generation tyrosine kinase inhibitor (TKI), a cost-effective first-line therapy for treatment-naive, epidermal growth factor receptor gene (*EGFR*)-mutated, non–small cell lung cancer?

Findings In this cost-effectiveness analysis of data from the FLAURA randomized clinical trial, the number of incremental quality-adjusted life-years (QALYs) gained in the base case by using osimertinib was 0.594 compared with using first- and second-generation EGFR-TKIs. In the United States, the incremental cost per QALY was approximately $225 000, and in Brazil, approximately $172 000.

Meaning At current costs, by World Health Organization cost-effectiveness threshold criteria, osimertinib is not cost-effective as a first-line therapy of *EGFR*-mutated NSCLC.

Methods

We developed a decision-analytic model using clinical data from the FLAURA randomized clinical trial.[9] The model compared 2 strategies for treating patients with advanced NSCLC and *EGFR* mutations: (1) the first-generation EGFR-TKIs followed by second-line osimertinib for those who harbor T790M mutation or other standard second-line therapies such as chemotherapy or immunotherapy for those who do not harbor the T790M mutation; (2) osimertinib in the first-line setting followed by standard second-line therapy at disease progression (eFigure 1A in the Supplement). We assumed that the clinical outcome results with afatinib are similar to those with gefitinib or erlotinib based on our prior meta-analysis.[11]

We analyzed data from the perspective of the US Medicare system and Brazilian private health system. We considered the costs for drug acquisition, supportive care in adverse events, and drugs prescribed after progression. Other direct costs such as monitoring and end-of-life costs were also considered.[12] Drug acquisition prices were based on American[13] and Brazilian data[14] widely available on the internet as of November 30, 2017. A 2% discount rate per year was considered in the analysis. We used the median PFS as the median treatment duration for each arm.

Brazilian reals were converted to US dollars to facilitate global cost standardization, based on an exchange rate of 3.25 Brazilian reals to 1.00 US dollar. In the United States, the monthly costs of osimertinib, erlotinib, gefitinib, and afatinib were $17 028.90, $9390.44, $9117.36, and $9785.72, respectively. In Brazil, these costs were $8789.96, $2127.60, $1029.94, and $1349.14, respectively.[14] The utility of each health state as well as the disutility of each relevant adverse event were obtained from the literature.[15,16]

The primary end point of this study was the incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life-year (QALY) gained by using osimertinib compared with first- or second-generation EGFR-TKIs for the treatment of previously untreated *EGFR*-mutated NSCLC.

Secondary end points were the highest price of osimertinib that still sustained high cost-effectiveness, the number of life-years saved, and the cost of each life-year saved. In addition, deterministic sensitivity analyses were performed to test the robustness of the results and to assess strategies that could improve cost-effectiveness, such as cost-sharing (2 first cycles free of charge) and risk-sharing (reimbursement of nonresponders' cost).

Model Structure

In the decision-analytic model, patients were classified into 3 mutually exclusive health states: progression-free disease, postprogression disease, and death.

Clinical Effectiveness and Quality of Life

Individual patient data on PFS and overall survival (OS) within the osimertinib and standard-of-care groups were extracted via the techniques outlined in Guyot et al,[17] and Kaplan-Meier graphs were created with WebPlotDigitizer.[18] For each

end point (PFS and OS) and each treatment arm (osimertinib and standard of care), event time distributions were estimated via a composite model, using the nonparametric Kaplan-Meier survival estimator up to last follow-up and the flexible parametric Weibull model for the tail, after last follow-up. Fitted composite models are shown in eFigure 1B in the Supplement. Notably, OS and PFS times can be estimated in the context of the composite models (Kaplan-Meier until last follow-up, then Weibull tail) without requiring a fixed time horizon.

The utility of progression-free disease and postprogression disease were calculated according to published utilities.[15,16] We did not consider different utilities for each treatment arm owing to the lack of quality-of-life data. However, the disutility due to the most frequent adverse events was considered.

Medical Costs

In addition to drug acquisition costs, we considered the costs of adverse events and supportive care, according to published data and corrected for inflation.[19-21] We also considered the treatment costs related to brain metastasis.[22] The costs of postprogression therapies were also considered according to the number of patients receiving each postprogression drug listed in the FLAURA study.

Deterministic Sensitivity Analysis

We performed several 1-way deterministic sensitivity analyses to assess the influence of uncertainty in individual input parameters on the ICER. We included the 95% confidence intervals (CIs) for the most important variables (eTable 1 in the Supplement) and assessed the probability of osimertinib being cost-effective based on a willingness-to-pay threshold of $180 000 per QALY in the United States or $35 000 in Brazil.

Results

Base Case Scenarios

For osimertinib, respective mean OS and PFS times were 47.7 months and 19.1 months, while for the standard of care, respective mean OS and PFS times were 35.6 months and 11.7 months. The incremental number of QALYs gained with osimertinib compared with first- and second-generation EGFR-TKIs in the base case, defined by the FLAURA findings, was 0.594. The number of incremental life-years saved in the base case was 1.01 (eTable 2 in the Supplement).

In the United States, the osimertinib ICER per QALY was $226 527 compared with erlotinib, $231 123 compared with gefitinib, and $219 874 compared with afatinib. In Brazil, the ICERs per QALY were $162 329, $180 804, and $175 432, respectively.

In the United States, the incremental cost per 1 life-year saved was $133 472 for erlotinib, $136 180 for gefitinib, and $129 552 for afatinib. In Brazil, the incremental costs per 1 life-year saved were $95 646, $106 532, and $103 366, respectively. eTable 2 in the Supplement summarizes the base case results.

Deterministic Sensitivity Analysis

The FLAURA trial data considered for this analysis is detailed in eTable 1 in the Supplement. The factor that had the strongest influence on incremental QALY was OS (95% CI) (ranging from 0.106 at the lower OS value to 1.029 at the higher OS value). The strongest influence on incremental cost was PFS (95% CI) (ranging from $35 701 at the lower PFS value to $179 284 at the higher PFS value; in Brazil these values were $50 366 and $137 759, respectively).

The next most important factor influencing osimertinib cost-effectiveness was hypothetical price discounts on osimertinib. Considering a willingness-to-pay threshold of $180 000 in the United States, and $30 000 in Brazil (equivalent to 3 times the gross domestic product per capita of each country, per World Health Organization cost-effectiveness threshold criteria[23]), the probability that osimertinib was cost-effective increased from 22.2% in the United States or 0% in Brazil (with no discounts) to 35.2% or 2.0% (with discounts), respectively. The maximum cost of osimertinib to be cost-effective was $12 500 in the United States and $3000 in Brazil. All deterministic sensitivity analyses are summarized in tornado diagrams for the United States and Brazil in eFigures 2 and 3, respectively, in the Supplement).

In summary, at current costs and considering the willing-to-pay thresholds, we found that osimertinib is unlikely to be cost-effective for *EGFR*-mutated first-line therapy in either the United States (17%, eFigure 4A in the Supplement) or Brazil (2%, eFigure 4B in the Supplement).

Discussion

New cancer drugs are being developed at an unprecedentedly rapid pace. From 2010 to 2013, more drugs were launched for cancer treatment than in the decade between 2000 and 2010,[24] and the monthly and total costs of these are also accelerating. In the United States, the average cost for new drugs for 1 year often exceeds $100 000.[25] As the cost of new anticancer drugs continues to increase at a double-digit percentage every year, the challenge of addressing extreme health care costs has become increasingly immediate.[26,27] For the present study, we chose representative high-income and higher-middle-income countries to assess the cost-effectiveness of osimertinib as a first-line treatment for patients with *EGFR*-mutated NSCLC.

Two prior studies have evaluated the cost-effectiveness of osimertinib as a second-line treatment for patients with *EGFR* T790M mutations. However, to our knowledge, the present study represents the first evaluation of osimertinib in the first-line setting. Wu et al[28] considered American and Chinese frameworks and demonstrated that osimertinib was not cost-effective in either setting. Furthermore, they concluded that decreases in osimertinib acquisition cost should enable cost-effectiveness. Bertranou et al[29] evaluated the cost-effectiveness of osimertinib in the United Kingdom, where drug acquisition costs are usually lower than in the United States. They found that the probability of osimertinib being a cost-

effective treatment was 63.4%, based on a threshold of £50 000 for each incremental QALY.

In the United States, the transparency of drug prices is limited, and the lack of federal control over drug prices leads to the highest drug costs in the world.[26] When different drug prices are evaluated according to per-capita spending power, anticancer drugs remain the most unaffordable category in economically developing countries, such as India and China.[30] In the present study, the monthly cost of osimertinib was 29% of the US gross domestic product per capita and 101% of the Brazilian gross domestic product per capita. Interestingly, in the United States, osimertinib costs less than twice as much as first- or second-generation TKIs, while in Brazil, it costs almost 9 times more than first- or second-generation TKIs. Consequently, the maximum cost of osimertinib to sustain cost-effectiveness in Brazil should not exceed $3000 per month, while in the United States, this maximum cost could reach up to $12 500 per month. This may lead to a disparity in lung cancer care between American and Brazilian patients.

Other strategies such as cost sharing or risk sharing did not make osimertinib cost-effective in either the United States or Brazil. Cost sharing (2 free treatment cycles) is likely ineffective owing to the long PFS (18.9 months) associated with osimertinib; the 2 free treatment cycles, lasting only a few months, may be relatively too short a treatment period.[9] And risk sharing may not be effective because only a small proportion of patients will be nonresponders (1%). Risk sharing is an interesting strategy for drugs with a low proportion of responders, such as immunotherapy for NSCLC second-line treatment.[31] In addition, risk sharing requires that a supervision system be incorporated and maintained, which carries its own set of costs.[32]

Limitations

A major limitation for cost-effectiveness studies is the necessary adoption of a specific set of circumstances than can never duplicate the wide range and dynamic nature of the real-world clinical scenario.[33] Cost-effectiveness studies are designed for a specific scenario at the time of policy makers' decisions, so detailed differences in scenarios may yield different cost-effective results.[33] In Brazil, for example, the socioeconomic disparity between the public and private health users is severe, and our study was developed exclusively based on the private health system. In Brazilian public health services, the first-generation TKIs are still unavailable.[34]

Another limitation of our study was that the 10-year OS estimate based on individual patient data from the FLAURA trial is still immature.[9] In the FLAURA study, patients in both arms had not yet reached their median OS at the time of the present analysis. In addition, the osimertinib treatment effect reported in FLAURA, represented by hazard ratio, remained above the limit previously planned for statistical significance previously at the time the work for the present study was completed. While we estimated 10-year OS based on individual patient data to provide the best available information, it is still too early to conclude whether osimertinib treatment will improve OS compared with first- and second-generation EGFR-TKIs.

Conclusions

In summary, despite being highly efficacious in the first-line treatment of patients with advanced *EGFR*-mutated NSCLC, osimertinib, due to its high cost, was not cost-effective in our model in either the United States or Brazil. In the United States, price negotiations and relatively small discounts of 10% to 20% would likely make it so. In Brazil, larger discounts or alternative strategies are necessary to improve access for a greater number of patients. All stakeholders in health care systems have the responsibility to be part of the solution. Our role as oncologists and researchers is to continue generating data and to communicate our findings to all relevant persons and institutions.

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Study concept and design: Aguiar, Park, Lopes.
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