ORIGINAL ARTICLE

Cost-Effectiveness of Adjuvant Osimertinib With and Without Chemotherapy for Surgically Resected NSCLC

Angelos Vasilopoulos, BS,[a] Alexander Pohlman, MD,[a,b,c] Ayham Odeh, MD,[a,b] K. Robert Shen, MD,[d] Julia M. Coughlin, MD,[a,b] Zaid M. Abdelsattar, MD, MS, FACS[a,b,e,*]

[a]*Stritch School of Medicine, Loyola University Chicago, Chicago, Illinois*
[b]*Department of Thoracic & CV Surgery, Loyola University Medical Center, Maywood, Illinois*
[c]*Department of Surgery, University of Illinois at Chicago, Chicago, Illinois*
[d]*Department of Surgery, Mayo Clinic, Rochester, Minnesota*
[e]*Department of Surgery, Edward Hines Jr. Medical Center, US Department of Veterans Affairs, Hines, Illinois*

Received 28 October 2024; revised 21 March 2025; accepted 30 March 2025
Available online - 9 April 2025

ABSTRACT

Introduction: Osimertinib is now approved as adjuvant therapy for stage IB to III NSCLC with *EGFR* mutations. Nevertheless, this treatment is lengthy and expensive. Its cost-effectiveness profile as monotherapy versus combination with chemotherapy is unknown. In this context, we investigate the cost-effectiveness of adjuvant osimertinib with and without chemotherapy for NSCLC.

Methods: A set of Markov models was established to predict the cost-effectiveness of these different regimens. Data were sourced from the ADAURA trial's publications and protocols. Health outcomes were quantified as quality-adjusted life-years (QALYs). Costs and incremental cost-effectiveness ratios (ICERs) were estimated in U.S. dollars (USD) and USD per QALY, respectively. Deterministic and probabilistic sensitivity analyses were performed. Data from the Surveillance, Epidemiology, and End Results Program were used to predict additional costs to the U.S. health care system.

Results: Compared with treatment with chemotherapy alone, treatment with osimertinib plus chemotherapy yielded 5.86 QALYs with incremental costs of $414,607.69 (ICER = $380,347.85 per QALY). Treatment with osimertinib alone yielded 6.63 QALYs with an incremental cost of $402,224.32 (ICER = $213,447.59 per QALY). Osimertinib is only likely to be cost-effective if the willingness-to-pay threshold per QALY is $200,000 or more. The price of osimertinib had the strongest influence on cost-effectiveness. On the basis of Surveillance, Epidemiology, and End Results Program data, these practices may cost the U.S. health care system an additional 8.9 billion USD/year.

Conclusions: Adjuvant osimertinib alone is more cost-effective than combination therapy, but only if the willingness-to-pay is high. A reduction in the price of osimertinib would improve its cost-effectiveness profile.

Keywords: Lung cancer; Targeted therapy; EGFR; Osimertinib; Cost-effectiveness

Introduction

The treatment of NSCLC has changed drastically over recent years, with numerous new targeted- and immunetherapies. Nevertheless, new drugs also portend higher costs to patients with varying abilities and willingness-to-pay (WTP). One such treatment modality for the treatment of *EGFR*-mutant NSCLC includes surgical resection

***Corresponding author.**

Mr. Vasilopoulos and Dr. Pohlman contributed equally to this work.

Address for correspondence: Zaid M. Abdelsattar, MD, MS, FACS. Department of Thoracic and CV Surgery, Loyola Univeristy Chicago, 2160 S First Avenue, Maywood, Illinois 60153. E-mail: zaid.abdelsattar@lumc.edu

Cite this article as: Vasilopoulos A, Pohlman A, Odeh A, et al. Cost-effectiveness of adjuvant osimertinib with and without chemotherapy for surgically resected NSCLC. *JTO Clin Res Rep*. 2025;6:100833.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2025.100833

followed by targeted therapy and chemotherapy. Implementation of adjuvant therapy has resulted in substantial improvements in the treatment of NSCLC and survival, but it is currently unclear what the most cost-effective strategy is.[1]

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), has proven effective in the treatment of advanced *EGFR* mutation-positive NSCLC.[2] This drug occupies an important space in the treatment of NSCLC as data shows that the risk of recurrence after adjuvant chemotherapy is higher among patients with EGFR-mutated NSCLC.[3,4] More recently, the ADAURA trial revealed that osimertinib is effective as adjuvant therapy for patients with EGFR-mutant resectable stage IB to III NSCLC.[3,5] The benefits of osimertinib have caused optimism among clinicians and patients and have led to widespread use of the drug.[6,7]

Nevertheless, a course of osimertinib lasts 3 years, and the cost of osimertinib is substantial, presenting a financial burden for patients and their families, which has become a topic of concern.[8] Thus far, the cost-effectiveness of osimertinib has been evaluated for first- and second-line treatment of advanced *EGFR*-mutated NSCLC,[9,10] and metastatic NSCLC,[11] but the cost-effectiveness profile with and without chemotherapy in the adjuvant setting of early-stage NSCLC is unknown.

In this context, we designed a set of Markov models to estimate the cost-effectiveness of osimertinib with and without cisplatin-pemetrexed therapy relative to cisplatin-pemetrexed therapy alone. In addition, we estimate the cost burden of this agent on the U.S. health care system annually. The study primarily takes on the perspective of U.S. payers, with the addition of supplementary data on overall costs to the U.S. health care system. The findings would have several implications for patients, payers, providers, and industry.

Materials and Methods

Model Structure

An irreversible Markov chain with time-varying transition probabilities was used to model the costs and quality-adjusted life-years (QALYs) accumulated over 10 years by patients treated with osimertinib with or without cisplatin-pemetrexed therapy. Six to eight weeks, or two Markov cycles, after resection, patients received cisplatin-pemetrexed for 3 months and osimertinib for 3 years, or only osimertinib for 3 years, consistent with recommended treatment schedules.[12]

The Markov model reflected the progression of patients in stages IB to IIIA between three disease states: alive without disease (A), alive with disease (AD), and dead, with all resected patients beginning in the A state. In each cycle, patients were redistributed among the states according to time-dependent probabilities (Fig. 1).

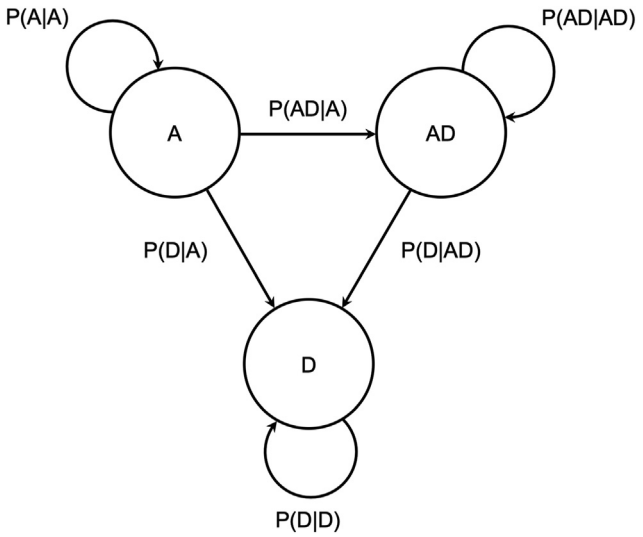

Figure 1. Three-health state Markov chain. All Markov models consisted of three states: A, AD, and D. All chains were irreversible with time-dependent transition probabilities. *P(a|b) represents the probability of transition to disease state a from disease state b. A, alive without disease; AD, alive with disease; D, dead.

Outcome measures were QALYs and costs accumulated over 10 years in U.S. dollars (USDs). Incremental cost-effectiveness ratios (ICERs) were determined from these as $ICER = \frac{cost_{osimertinib+cisplatin-pemetrexed} - cost_{cisplatin-pemetrexed}}{QALYs_{osimertinib+cisplatin-pemetrexed} - QALYs_{cisplatin-pemetrexed}}$ representing the additional costs incurred per QALY gained.

Data Collection and Model Fitting

Overall survival (OS) and disease-free survival data from the ADAURA trial were extracted from published Kaplan-Meier curves using the peer-reviewed digitization software WebPlotDigitizer.[3,13] Subsequently, the IPDfromKm algorithm developed by Liu et al.[14] was used to estimate individual patient data.

Parametric curves—Weibull, exponential, Gaussian, lognormal, and log-logistic—were fitted to survival data and used to extrapolate survival to a 10-year time horizon. Best-fit curves were selected according to the Akaike information criterion, shown for each curve in Table 1, with a lower Akaike information criterion indicating a better fit. The parameters of the fitted parametric curves were used to estimate transition probabilities for a time-varying, irreversible Markov model using the Weibull survival function $S_{Weibull}(t) = exp(-\lambda t^{\gamma})$

and the lognormal survival function $S_{lognormal}(t) = 1 - \Phi(log(t) - \mu)/\sigma$, t equal to time; γ, λ, μ, and σ are distribution-specific parameters (Table 2); and Φ is the normal density function.

All probabilities were time-dependent and varied from one cycle to the next, except for the probability of

Table 1. AIC Values of Fitted Parametric Curves

	Osimertinib + Chemo		Osimertinib Alone		Chemo Alone	
Distribution Model	DFS	OS	DFS	OS	DFS	OS
Exponential	278.8168	347.4202	180.1629	218.9913	898.6504	622.3874
Gaussian	272.2885	333.8092	178.9537	220.0999	961.3951	622.6171
log-logistic	269.2758	329.8332	175.0834	215.2877	886.9021	610.0694
lognormal	270.3476	327.972[a]	174.6729[a]	213.8605[a]	879.4258[a]	609.0137[a]
Weibull	268.9449[a]	330.3164	175.2706	215.5344	895.6298	610.8831

Note: The AIC was used as the criterion for model selection, with a lower AIC indicating a better fit.
[a]Best fit AIC for each case: Osimertinib plus chemotherapy DFS (Weibull, 268.9449), osimertinib plus chemotherapy OS (lognormal, 327.972), osimertinib alone DFS (lognormal, 174.6729), osimertinib alone OS (lognormal, 213.8605), chemotherapy alone DFS (lognormal, 879.4258), chemotherapy alone OS (lognormal, 609.0137).
AIC, Akaike information criterion; Chemo, chemotherapy; DFS, disease-free survival; OS, overall survival.

progression from state A to the dead state, which was assumed to resemble the probability of death in the general population and was constant.[15]

Our evaluation of cost-effectiveness comprised three parts: a base-case analysis, in which cost-effectiveness was evaluated holding all model variables constant at their most likely values; a one-way deterministic sensitivity analysis, in which the change in cost-effectiveness was observed with "one-at-a-time" changes in model parameters like drug prices and health state utility values; and probabilistic sensitivity analysis, in which changes in the probability of cost-effectiveness were observed with simultaneous changes in the same model parameters.

Costs and Utilities

Health state costs were sourced from drug pricing information provided by the Memorial Sloan-Kettering Cancer Center and utilities were collected from a report of EuroQoL five-dimension survey results from Nafees et al.[16,17] A weighted average of utility values for alive with stable disease and alive with progressive disease was used to create a combined utility value for the AD state. This weighted average was created using local disease recurrence as a surrogate for "alive with stable disease" and metastatic disease as a surrogate for "alive with progressive disease" as reported in an ADAURA follow-up study.[18] Health state costs and utilities were summed appropriately over a 10-year period with respect to monthly health state distributions. A discounting rate of 3% per annum was used for drug pricing. An ICER was calculated to compare osimertinib plus chemotherapy versus adjuvant chemotherapy alone and osimertinib versus adjuvant chemotherapy alone.

Sensitivity Analysis

To determine the reliability of our model, one-way and probabilistic sensitivity analyses were performed. In one-way sensitivity analysis, each model parameter was increased and reduced by 10% with all other parameters constant, and consequent changes in ICER were noted. A 50% reduction in the price of osimertinib was also simulated. In probabilistic sensitivity analysis, model parameters were varied simultaneously and randomly in 1000 simulations, and consequent changes in ICERs were noted. Parameters analyzed included the Γ-distributed prices of osimertinib, pemetrexed, and cisplatin; and the β-distributed utilities of disease-free and diseased survival. The Memorial Sloan-Kettering Cancer Center reports the prices of osimertinib, cisplatin, and pemetrexed in the United States as

Table 2. Distributions and Parameters of Selected Models

	DFS		OS	
Treatment Groups	Distribution	Parameters	Distribution	Parameters
Osimertinib + chemo	Weibull	$\lambda = 0.000172$ $\gamma = 2.033956$	Lognormal	$\mu = 4.964532$ $\sigma = 0.719797$
Osimertinib	Lognormal	$\mu = 5.355292$ $\sigma = 1.038708$	Lognormal	$\mu = 4.457521$ $\sigma = 1.00461$
Cisplatin-pemetrexed	Lognormal	$\mu = 4.863949$ $\sigma = 1.037622$	Lognormal	$\mu = 3.087584$ $\sigma = 1.094467$

All Kaplan-Meier curves were best fitted by lognormal curves, except for the DFS curve of patients receiving osimertinib plus adjuvant chemotherapy, which was best fitted by a Weibull curve. Parameters for the curves with best fit were estimated using the R function survival::survreg.
λ, shape; γ, scale; μ, log-mean; σ, log-scatter; DFS, disease-free survival; OS, overall survival.

$12,750.00, $125.00, and $5086.00 per month, respectively, which were used for the purposes of this study (Table 3).[17,19]

Evaluation of National Data

Surveillance, Epidemiology, and End Results Program data, encompassing approximately 47.9% of the U.S. population from 2021, revealed 42,318 new cases of stage IB to III NSCLC.[20] Exon 19 deletions and exon 21 L858R mutations, which encompass most *EGFR* mutations, are susceptible to osimertinib therapy. Prevalence of these mutations varies by study, but they are estimated to be present in approximately 22% of newly diagnosed lung cancers in the United States[21] These current figures were used in conjunction with the monthly cost of osimertinib to estimate the total cost of a 3-year course of osimertinib for predicted patients diagnosed with *EGFR*-mutant lung cancers to the U.S. health care system.

To evaluate the effect of chemotherapy on survival in this patient population, we used the National Cancer Database (NCDB) to assess OS rates between patients receiving adjuvant chemotherapy and those who did not.[22] The same inclusion criteria that were used in the ADAURA trial were used to create the patient cohort. This included patients with *EGFR* exon 19 or 21 mutations, stage I to III NSCLC, complete resection with a minimum of lobectomy, and patients who did not receive radiation. Only patients diagnosed in or after 2021 were included because EGFR data are not available before that time in the NCDB. Patients were divided into two groups: those who received adjuvant chemotherapy and those who did not. Kaplan-Meier survival and log-rank test were used to assess OS.

Results

In the base-case analysis over a 10-year period, treatment with osimertinib plus chemotherapy resulted in 5.86 QALYs and an incremental cost of $414,607.69 (ICER = $380,347.85 per QALY) per patient compared with treatment with pemetrexed-cisplatin alone. Treatment with osimertinib alone yielded 6.63 QALYs with an incremental cost of $402,224.32 (ICER = $213,447.59 per QALY) per patient. A Weibull curve was the best fit to the curve of disease-free survival of patients on osimertinib plus adjuvant chemotherapy, whereas a lognormal curve was the best fit for all other scenarios. The shape (λ) and scale (γ) parameters were estimated for the Weibull curve, and log-mean (μ) and log-scatter (σ) parameters were estimated for the lognormal curves. A report from Nafees et al.[16] provided annual health state utilities. Patients with state A of the disease had a utility of 0.883 QALYs. As mentioned in the methods section, a weighted average utility value of 0.466 was used for the AD state to account for both alive with stable disease and alive with progressive disease. All utility values were divided by 12, as the Markov model cycle length was 1 month.

In one-way sensitivity analysis, successive, or "one-at-a-time," 10% reductions and increases of prices and utilities were used to determine the influence of each model parameter on ICERs. Figure 2 reports a tornado plot showing ICERs for the 10% reduction and increase of each model parameter, which illustrates that the predominant influence on the ICER of osimertinib plus chemotherapy was the utility of the disease-free state, followed by the cost of osimertinib; the predominant influence of osimertinib alone on the ICER was the price of osimertinib. Figure 3 reports the visual comparison of

Table 3. Model Parameter Base Values and Distributions for Sensitivity Analysis

Model parameter	Base (range)	Distribution	Distribution parameters	Citation
Costs (USD)				
Osimertinib	12,750.00 (6726.02-23,737.43)	Γ	shape = 25 scale = base/shape	17
Cisplatin	125.00 (53.32-206.52)	Γ	shape = 25 scale = base/shape	17
Pemetrexed	5086.00 (2630.77-8264.84)	Γ	shape = 25 scale = base/shape	17
Utilities (QALYs)				
A	0.883 (0.731-0.962)	β	shape $\alpha = 100 \times$ base shape $\beta = 100 \times (1 -$ base)	16
AD	0.466 (0.315-0.608)	β	shape $\alpha = 100 \times$ base shape $\beta = 100 \times (1 -$ base)	16
D	0.00			

Drug prices were sourced from the Memorial Sloan-Kettering Cancer Center. Health state utilities were sourced from a report of EQ-5D survey results by Nafees et al.[16] For one-way sensitivity analysis, the prices of osimertinib, cisplatin, and pemetrexed, and the utilities of disease-free and postprogression survival were varied by plus or minus 10% one at a time. For probabilistic sensitivity analysis, costs were modeled by Γ distributions and utilities by β distributions, as is common practice in cost-effectiveness analyses. For gamma distributions, the shape parameter α was set to 25, resulting in a SD equal to 20% of the mean. A, alive without disease; AD, alive with disease; D, dead; EQ-5D, EuroQoL five-dimension; USD, U.S. dollar.

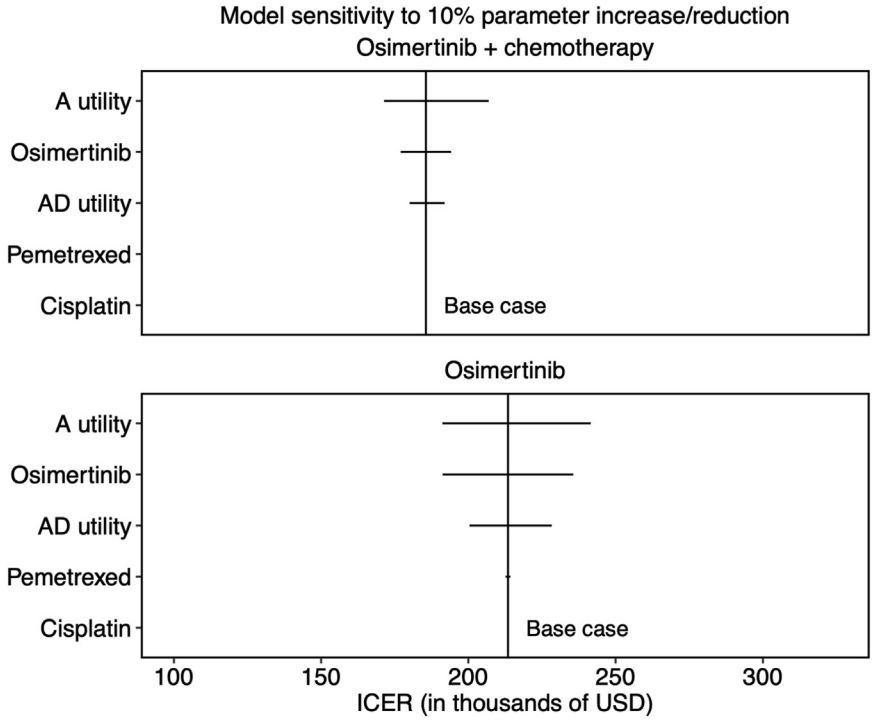

Figure 2. Tornado plots. The tornado plots depict the sensitivity of cost-effectiveness, measured as an ICER, to the variables of our model. Broader segments indicate greater sensitivity. In the case of treatment with osimertinib and adjuvant chemotherapy, the ICER was most sensitive to the utility of the A state and then the price of osimertinib. In the case of treatment with osimertinib alone, the ICER was most sensitive to the price of osimertinib and then the utility of the A state. A, alive without disease; AD, alive with disease; ICER, incremental cost-effectiveness ratio.

the effects of drug pricing on the ICER in each treatment case. A 50% price reduction created an ICER of $190,428.38 per QALY for osimertinib with chemotherapy and an ICER of $102,613.63 per QALY for osimertinib alone.

In probabilistic sensitivity analysis, we observed the cost-effectiveness of the treatments of interest in 1000 simulations. Figure 4*A* is a visual representation of those simulations. Each point on the plot represents a single simulation of incremental cost and incremental effectiveness. Points below the WTP thresholds represent cost-effective simulations, whereas points above the lines represent cost-ineffective simulations. More points below a lower WTP threshold indicate a greater probability of a treatment being within the bounds of cost-effectiveness. In the case of treatment with osimertinib plus chemotherapy, most simulations fell above the WTP threshold of $200,000.00 per QALY. In the case of treatment with osimertinib alone, simulations were relatively more cost-effective. As shown in Figure 4*B*, as the WTP threshold increases, the probabilities of osimertinib plus chemotherapy and osimertinib alone being cost-effective treatments increase. Nevertheless, the WTP must be increased more in the case of combined treatment to see similar increases in the probability of cost-effectiveness.

National Data Analysis

Given 42,318 new reported cases of stage IB to III lung cancer found in Surveillance, Epidemiology, and End Results Program data from 2021, encompassing approximately 47.9% of the population, estimates for the entire U.S. population for the year would be 88,346 patients. Approximately 22% of these are estimated to have targetable *EGFR* mutations. Thus, approximately 19,436 new patients would be eligible for adjuvant osimertinib therapy. Given the current cost of osimertinib, $12,750/month or $459,000 for a 3-year course, this incurs an additional total cost of $8.9 billion to the U.S. health care system.

Analysis of NCDB data found 1992 patients who met inclusion criteria, of which 887 (44.5%) received adjuvant chemotherapy and 1105 (55.5%) did not. Survival over the available time period among all patients with stage I to III disease was equivalent between the two groups (88.0% without chemotherapy versus 88.4% with chemotherapy, $p = 0.847$). A treatment guideline by the American Society of Clinical Oncology recommended adjuvant chemotherapy only for stage II to III disease, so this was analyzed separately.[12] After excluding patients with stage I disease, there were 795 patients with stage II or III disease, of which 637 (80.1%) received adjuvant chemotherapy and 158 (19.9%) did not. There was a

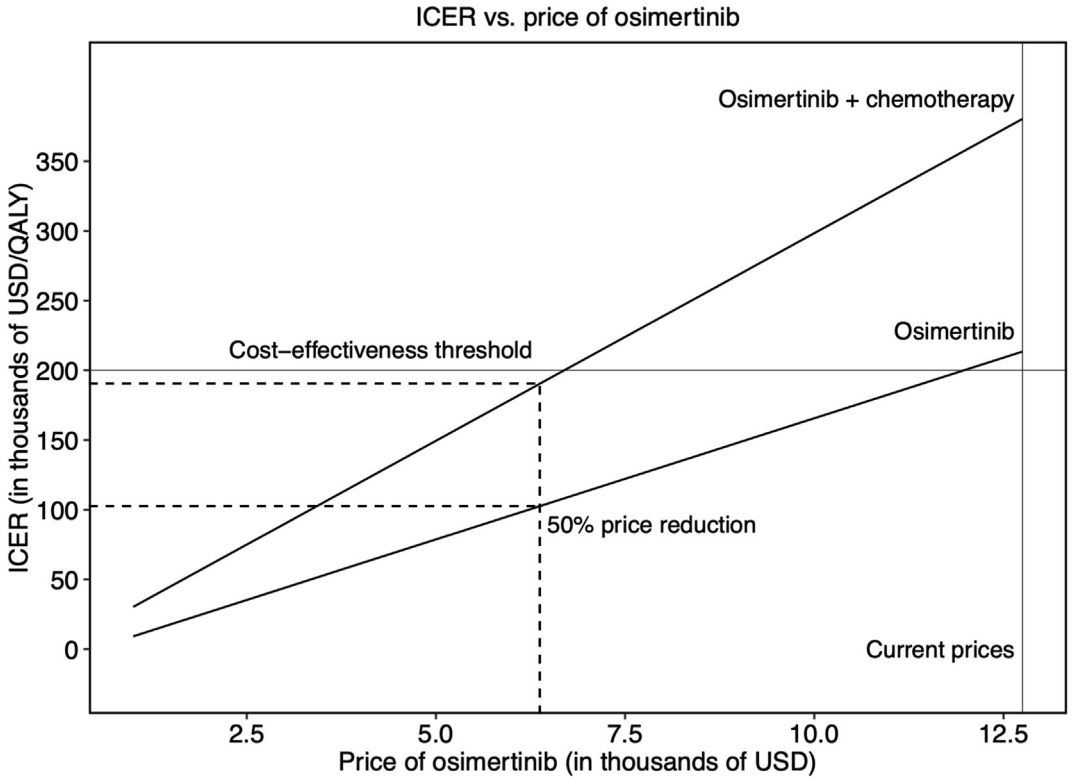

Figure 3. One-way sensitivity analysis of ICER to the price of osimertinib. The ICER of the ADAURA trial regimen, given with adjuvant chemotherapy or alone, increases as the price of osimertinib increases. A 50% reduction in price would reduce the ICER of combined therapy to $190,428.38 per QALY and the ICER of treatment without adjuvant chemotherapy to $102,613.63 per QALY. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; USD, U.S. dollar.

survival advantage for patients with stage II to III disease receiving chemotherapy, as OS was 88.9% in this group compared with 68.2% in the group without chemotherapy ($p = 0.008$).

Discussion

In this cost-effectiveness analysis (CEA) of the ADAURA trial regimen comparing treatment with osimertinib plus chemotherapy and osimertinib alone to treatment with a common doublet chemotherapy for resected NSCLC in the United States, we found the following: (1) the price of osimertinib is one of the predominant influences on the cost-effectiveness of the ADAURA regimen for the treatment of NSCLC; (2) administration of osimertinib alone is a more cost-effective regimen than combination with chemotherapy but only at a high WTP threshold; and (3) at current pricing, the U.S. health care system would spend $8.9 billion annually on osimertinib alone for predicted eligible patients.

The price of osimertinib and the utility of the disease-free state had the most dramatic effects on ICERs in both instances, osimertinib alone and osimertinib with chemotherapy. This suggests that the price of osimertinib is a promising target for reducing the overall cost of adjuvant treatment with the ADAURA regimen. Indeed, osimertinib costs approximately twice as much in the United States as it does in the People's Republic of China and some European countries.[23,24] Nevertheless, based on our study results, a price reduction would have to be substantial for combined therapy to become cost-effective, as even with a 50% price reduction, at $190,428.38 per QALY, the ICER of combined therapy remains above some of the recommended cost-effectiveness thresholds.

Similar studies have used a wide range of cost-effectiveness thresholds from $50,000.00 to $250,000.00 per QALY. An often used threshold is three times the per capita annual gross domestic product,[25] which is approximately $200,000.00 per QALY in the case of the United States as of 2024.[26] At the same time, the Institute for Clinical and Economic Review suggests a threshold of $50,000.00, $100,000.00, $150,000.00, or $200,000.00 per QALY.[27] Given this range of thresholds, the results of this analysis suggest that, at current prices, treatment with osimertinib plus chemotherapy is not cost-effective for patients with resected NSCLC, even at the highest cost-effectiveness threshold, but osimertinib monotherapy may be cost-effective given the increase in

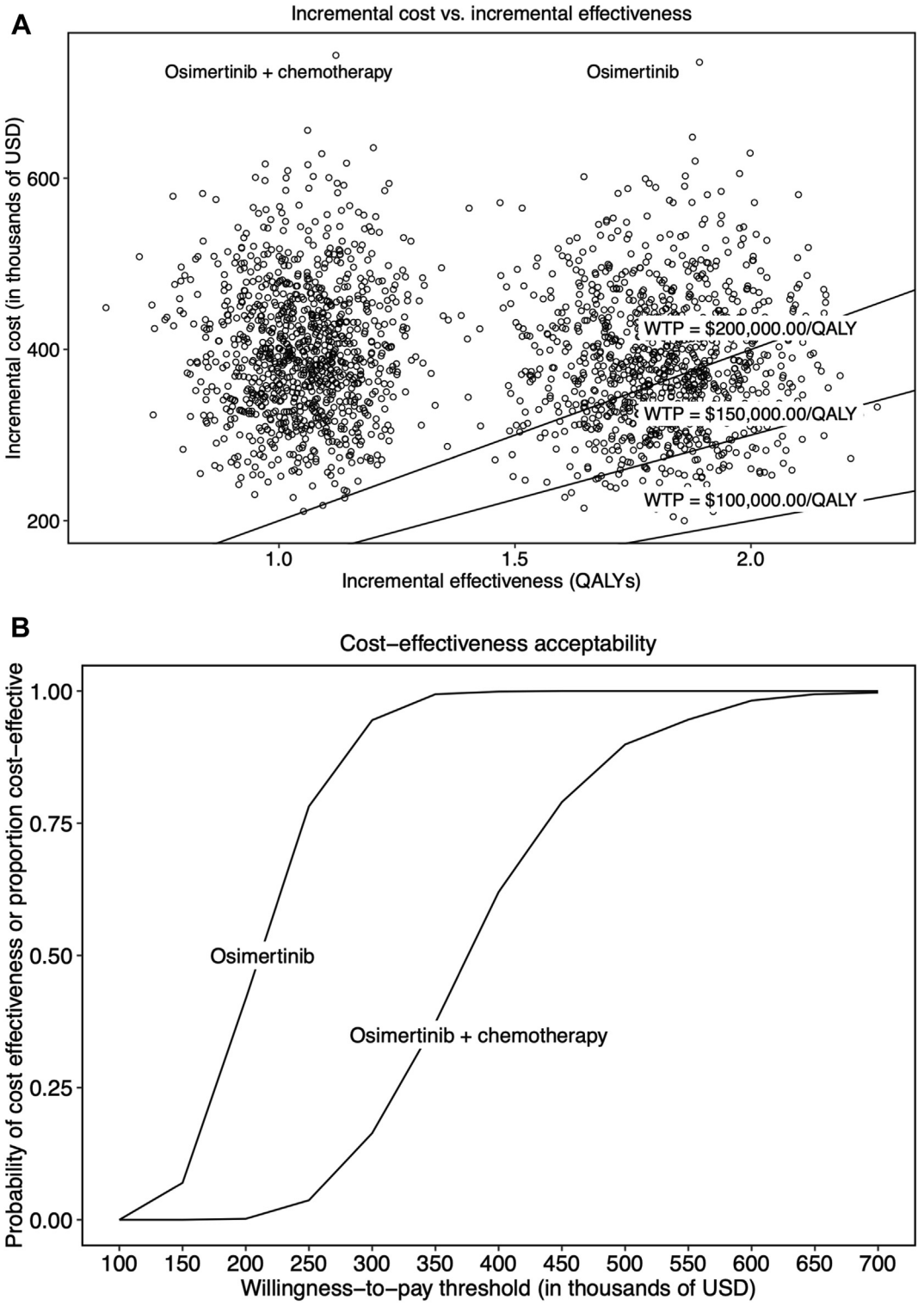

Figure 4. *(A)* Plot of PSA simulations. Points falling above the WTP lines represent simulations in which treatment was not cost-effective, whereas points falling below represent simulations in which treatment was cost-effective. *(B)* Probability of cost-effectiveness versus WTP. As the WTP threshold increases, simulations of expensive treatments are more likely to seem cost-effective. The more the WTP threshold has to be increased for a treatment to reach a certain cost-effectiveness, the less likely the treatment is to be cost-effective. PSA, probabilistic sensitivity analysis; WTP, willingness-to-pay. USD, U.S. dollar.

QALYs. Nevertheless, the price of osimertinib can drastically change these results.

There have been several other studies evaluating the cost-effectiveness of osimertinib alone in comparison to placebo, erlotinib, and other chemotherapy regimens. When comparing osimertinib alone versus placebo, the results change drastically depending on the cost of the reference drug and the source country. One Chinese CEA using ADAURA trial data found an osimertinib to placebo ICER of $9661.00 per QALY.[28] Similarly, a Canadian-based CEA found an ICER of $35,811.00 per QALY when comparing osimertinib alone to surveillance.[29] This is in stark contrast to United States–based CEAs, which indicate ICERs greater than $300,000.00 per QALY.[30,31]

Before the current study, osimertinib had only been compared with chemotherapy regimens as second or third-line therapy and on the basis of price points in countries outside the United States. A United Kingdom–based CEA compared osimertinib with a platinum-based doublet chemotherapy regimen as second-line therapy and revealed an ICER of £41,705 per QALY.[32] A Chinese-based CEA comparing osimertinib to docetaxel-bevacizumab as third-line treatment suggested an ICER of $25,947.00 to $30,264.00 per QALY.[33] Thus, yet again, we have multiple studies showing a high likelihood of cost-effectiveness outside the United States.

As previously stated, osimertinib has been shown to have superior survival benefits when compared with first and second-generation EGFR TKIs, such as erlotinib.[34,35] Nevertheless, previous CEAs comparing osimertinib to erlotinib found, almost universally, that osimertinib was not cost-effective owing to significantly higher costs and only mild increases in QALY.[8,23,36,37] Nevertheless, one study found that a price drop of only 5% could make osimertinib cost-effective compared with erlotinib,[9] and another study revealed that it may be more cost-effective as second-line therapy after erlotinib with or without chemotherapy in the advanced setting.[38]

Our probabilistic sensitivity analysis found that most simulations of combined therapy were not cost-effective, falling above the WTP lines. Nevertheless, although treatment with osimertinib plus adjuvant chemotherapy is very unlikely to be cost-effective, even at high WTP, treatment with osimertinib alone is more likely to be cost-effective at the same WTP thresholds by comparison.

This then begs the question of whether or not it is valid to compare osimertinib with chemotherapy to osimertinib alone. Ultimately, this is a complex question requiring more knowledge of chemotherapy's effect on survival in this patient population. Although the original ADAURA trial did not specifically address osimertinib alone versus osimertinib with chemotherapy, a subsequent analysis of ADAURA results looked at these two treatment regimens and found no significant benefit of chemotherapy in osimertinib-based adjuvant therapy for all disease states.[39] In addition, other studies have shown that cisplatin-based chemotherapy carries an absolute increase in 5-year survival rate of approximately 5%, and a prior review deemed its use in conjunction with osimertinib to be "debatable and subjective."[40,41]

We aimed to further explore this question using data from the NCDB. Our analysis of survival data on patients eligible for adjuvant osimertinib found that when comparing stages I to III, chemotherapy created no difference in survival. When excluding patients with stage I NSCLC, patients with stage II and III disease seemed to benefit from chemotherapy in this group. Nevertheless, the NCDB does not provide data on which EGFR TKI a patient received, so there is potential room for error in this analysis, and thus does not provide a definitive answer. In addition, these results differ from those obtained from the analysis of ADAURA data published by Li et al.,[39] in which no difference was found. Therefore, despite current treatment guidelines, the benefit of combination chemotherapy is still unclear.[12] We argue that the questionable utility and increased costs associated with chemotherapy may influence providers' decisions to include it in the treatment regimen with Osimertinib, particularly for stage I disease. Nevertheless, as shown in our analysis, a price reduction of osimertinib by 50% could avert this conundrum in both the case of osimertinib alone and the case of osimertinib plus chemotherapy.

On a larger scale, expansion of osimertinib treatment to all eligible patients, including stage IB to III, would create a significant financial burden for the U.S. health care system of $8.9 billion for 3 years of treatment. This is approximately 1% of total U.S. spending on prescription drugs in 2023 ($722.5 billion),[42] more than the National Cancer Institute's entire budget for 2024 ($7.22 billion),[43] and more than six times the total U.S. spending on lung cancer treatment in 2019 ($1.35 billion).[44]

This study has several limitations. First, per the ADAURA protocol, cisplatin-pemetrexed was not the only doublet therapy used in the trial. Nevertheless, it is among the most common doublet therapies given post-resection for NSCLC,[45] so all calculations were made using the prices of cisplatin-pemetrexed when a reference case was needed. Second, the Medicare reimbursement price of osimertinib was used for the purposes of this study, but this price may vary depending on the payer. Medicare costs are typically set at 106% of the average sales price, so some variability in this cost may be present depending on insurance.[17] As noted previously, the cost of osimertinib had one of the

greatest impacts on cost-effectiveness, so changes in insurance reimbursement could significantly alter outcomes of the study. Third, variability in health state utility values sourced from literature is important to note, especially considering the strong influence of the utility of the disease-free state on our model outputs. Fourth, this study did not incorporate the cost of treating side effects or the costs of administration of these drugs, particularly regarding chemotherapy. These were not included owing to the large variation in these costs and the lack of available data on the rates of side effects with osimertinib use. Other studies that did include these costs recognized that they may not accurately reflect real-world scenarios.[30] Therefore, this will be an important source of future study. We suspect that the addition of these costs would decrease the ICER of the osimertinib monotherapy group but remain stable for the osimertinib plus chemotherapy group owing to the suspected higher costs of treating chemotherapy side effects and complications. Fifth, extrapolation of patient outcomes past the end of the ADAURA trial is not without error. Although parametric curve-fitting is a long-standing practice and often a very accurate predictive tool,[46] extrapolations reflect hypothetical scenarios that are not always accurate.[47,48] Finally, in this analysis, we considered quality of life only as a function of disease state owing to the unavailability of health state utility values specific to both the drug and condition of interest in the literature (i.e., specific to both osimertinib and NSCLC). Although this is common practice in cost-effectiveness analyses, there is variability in quality of life associated with different therapeutics (e.g., osimertinib versus cisplatin-pemetrexed).[49] That is, the ICER of osimertinib treatment may have been underestimated if osimertinib causes less severe adverse side effects than cisplatin-pemetrexed, or overestimated if it causes more severe adverse side effects.

Notwithstanding these limitations, we believe our results are unique because, in addition to an urgently needed economic evaluation of a widely used medication, our analysis offers a high-resolution comparison of potential modalities of osimertinib administration, that is, in combination with other drugs or alone. The results might inform future clinical decision-making in the context of NSCLC treatment.

In conclusion, compared with treatment with cisplatin-pemetrexed in the U.S. setting, osimertinib with chemotherapy is unlikely to be cost-effective for the treatment of NSCLC, whereas osimertinib monotherapy is a more cost-effective treatment than combined therapy. For this reason, osimertinib alone is a better treatment option from a financial standpoint. Nevertheless, in both cases, a reduction in the price of osimertinib would improve cost-effectiveness and limit the financial burden on patients and their families.

CRediT Authorship Contribution Statement

Angelos Vasilopoulos: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing.

Alexander Pohlman: Data curation, Formal analysis, Investigation, Validation, Writing - original draft, Writing - review & editing.

Ayham Odeh: Data curation, Formal analysis, Writing - original draft.

K. Robert Shen: Methodology, Writing - original draft, Writing - review & editing.

Julia Coughlin: Methodology, Writing - original draft, Writing - review & editing.

Zaid M. Abdelsattar: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing – review & editing.

Disclosure

The authors declare no conflict of interest.

References

1. Valagussa P. History of adjuvant therapy. *Cancer Treat Res*. 2009;151:3–12.
2. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4:1046–1061.
3. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med*. 2023;389:137–147.
4. Kim H, Park S, Jung HA, et al. EGFR mutation-positive unresectable Stage III non-squamous lung cancer is associated with a high incidence of brain metastasis. *Cancer Res Treat*. 2023;55:498–505.
5. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383:1711–1723.
6. Ferro A, Marinato GM, Mulargiu C, et al. The study of primary and acquired resistance to first-line osimertinib to improve the outcome of EGFR-mutated advanced non-small cell lung cancer patients: the challenge is open for new therapeutic strategies. *Crit Rev Oncol Hematol*. 2024;196:104295.
7. Chen CH, Chou DW, Chung KM, Chang HY. EGFR tyrosine kinase inhibitor efficacy in older adult patients with advanced EGFR-mutated non-small-cell lung cancer: a meta-analysis and systematic review. *Medicina (Kaunas)*. 2022;58:1645.
8. Nargesi S, Dolatshahi Z, Rezapour A, et al. Cost-effectiveness of osimertinib in the treatment of advanced EGFR-mutated non-small cell lung cancer: a systematic

review. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22:543–554.
9. Shu Y, Ding Y, He X, Liu Y, Wu P, Zhang Q. Cost-effectiveness of osimertinib versus standard EGFR-TKI as first-line treatment for EGFR-mutated advanced non-small-cell lung cancer in China. *Front Pharmacol*. 2022;13:920479.
10. Li W, Qian L, Li W, et al. Cost-effectiveness analysis of different sequences of osimertinib administration for epidermal growth factor receptor-mutated non-small-cell lung cancer. *Exp Ther Med*. 2021;21:343.
11. Wu B, Gu X, Zhang Q. Cost-Effectiveness of Osimertinib for EGFR Mutation-Positive non-small Cell Lung Cancer after Progression following First-Line EGFR TKI Therapy. *J Thorac Oncol*. 2018;13:184–193.
12. Pisters K, Kris MG, Gaspar LE, Ismaila N. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA NSCLC Guideline Expert Panel. Adjuvant systemic therapy and adjuvant radiation therapy for stage I-IIIA completely resected non-small-cell lung cancer: ASCO guideline rapid recommendation update. *J Clin Oncol*. 2022;40:1127–1129.
13. Drevon D, Fursa SR, Malcolm AL. Intercoder reliability and validity of WebPlotDigitizer in extracting graphed data. *Behav Modif*. 2017;41:323–339.
14. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2021;21:111.
15. Ahmad FB, Cisewski JA, Xu J, Anderson RN. Provisional mortality data - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72:488–492.
16. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non-small cell lung cancer: an international study. *Asia Pac J Clin Oncol*. 2017;13:e195–e203.
17. Center for Health Policy and Outcomes. Price and Value of Cancer Drugs. Memorial Sloan-Kettering Cancer Center. www.mskcc.org/research-programs/health-policy-outcomes/cost-drugs. Accessed April 24, 2025.
18. Herbst RS, Wu YL, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer: updated results from the Phase III randomized ADAURA trial. *J Clin Oncol*. 2023;41:1830–1840.
19. Picot J, Cooper K, Bryant J, Clegg AJ. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. *Health Technol Assess*. 2011;15:1–204.
20. Surveillance, epidemiology, and end results (SEER [Program] (www.seer.cancer.gov/seerstate/) SEER*Stat Database: Incidence - SEER Research Limited-Field Data, Vol. 22. *Registries*; 2023 Sub (2000–2021), National Cancer Institute, DCCPS, Surveillance Research Program. *2023 Submission* November; released 2024
21. Zhang YL, Yuan JQ, Wang KF, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7:78985–78993.
22. Surgeons ACo. National Cancer Database. https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/puf/ Last accessed: April 24, 2025
23. Wu B, Gu X, Zhang Q, Xie F. Cost-effectiveness of osimertinib in treating newly diagnosed, advanced EGFR-mutation-positive non-small cell lung cancer. *Oncologist*. 2019;24:349–357.
24. Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol*. 2020;21:664–670.
25. Bertram MY, Lauer JA, De Joncheere K, et al. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ*. 2016;94:925–930.
26. *U.S. Bureau of Economic Analysis. Real Gross Domestic Product Per Capita*. St Louis: Federal Reserve Bank; 2024. Accessed April 24, 2025.
27. ICER 2019. Perspectives on cost-effectiveness threshold ranges. Institute for Clinical and Economic Review. www.icer.org/wp-content/uploads/2023/08/ICER_2019_Perspectives-on-Cost-Effectiveness-Threshold-Ranges.pdf. Accessed April 24, 2025.
28. Zhou X, Du J, Xu G, Chen C, Zheng B, Chen J. Cost-effectiveness of osimertinib versus placebo in resected EGFR-mutated non-small cell lung cancer in China. *Cancer Med*. 2022;11:4449–4456.
29. Verhoek A, Cheema P, Melosky B, et al. Evaluation of cost-effectiveness of adjuvant osimertinib in patients with resected EGFR mutation-positive non-small cell lung cancer. *Pharmacoecon Open*. 2023;7:455–467.
30. Lemmon CA, Zabor EC, Pennell NA. Modeling the cost-effectiveness of adjuvant osimertinib for patients with resected EGFR-mutant non-small cell lung cancer. *Oncologist*. 2022;27:407–413.
31. Huo G, Song Y, Liu W, Cao X, Chen P. Osimertinib in the treatment of resected EGFR-mutated non-small cell lung cancer: a cost-effectiveness analysis in the United States. *Front Pharmacol*. 2024;15:1300183.
32. Bertranou E, Bodnar C, Dansk V, Greystoke A, Large S, Dyer M. Cost-effectiveness of osimertinib in the UK for advanced EGFR-T790M non-small cell lung cancer. *J Med Econ*. 2018;21:113–121.
33. Rui M, Li H. Cost-effectiveness of osimertinib vs docetaxel-bevacizumab in third-line treatment in EGFR T790M resistance mutation advanced non-small cell lung cancer in China. *Clin Ther*. 2020;42:2159–2170.e6.
34. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.
35. Cheng Y, He Y, Li W, et al. Osimertinib versus comparator EGFR TKI as first-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, a randomized study. *Target Oncol*. 2021;16:165–176.
36. Khoo T, Gao L. Cost-effectiveness of osimertinib versus standard EGFR-TKI as first-line treatment for locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer in Australia. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21:415–423.
37. Aguiar PN Jr, Haaland B, Park W, San Tan P, Del Giglio A, de Lima Lopes G. Cost-effectiveness of osimertinib in the first-line treatment of patients with EGFR-mutated advanced non-small cell lung cancer. *JAMA Oncol*. 2018;4:1080–1084.
38. Cai H, Zhang L, Li N, et al. Cost-effectiveness of osimertinib as first-line treatment and sequential therapy

for EGFR mutation-positive non-small cell lung cancer in China. *Clin Ther*. 2019;41:280–290.
39. Li F, Zhao Y, Zhong R, et al. No benefit of chemotherapy in Osimertinib-treated postoperative non-small cell lung cancer patients. *Transl Lung Cancer Res*. 2021;10:3689–3693.
40. Maione P, Salvi R, Gridelli C. The role of adjuvant chemotherapy before osimertinib in epidermal growth factor receptor mutant resected non-small cell lung cancer and communicating it to patients. *Curr Oncol*. 2024;31:987–997.
41. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. *Transl Lung Cancer Res*. 2015;4:191–197.
42. Tichy EM, Hoffman JM, Tadrous M, et al. National trends in prescription drug expenditures and projections for 2024. *Am J Health Syst Pharm*. 2024;81:583–598.
43. Ledford H. Budget cuts hit world's largest cancer-research funder: what it means for scientists [e-pub ahead of print]. *Nature*. 2025. https://doi.org/10.1038/d41586-024-02978-2. accessed July 1, 2024.
44. Yabroff KR, Mariotto A, Tangka F, et al. Annual report to the nation on the status of cancer, part 2: patient economic burden associated with cancer care. *J Natl Cancer Inst*. 2021;113:1670–1682.
45. Désage AL, Tissot C, Bayle-Bleuez S, et al. Adjuvant chemotherapy for completely resected IIA-IIIA non-small cell lung cancer: compliance to guidelines, safety and efficacy in real-life practice. *Transl Lung Cancer Res*. 2022;11:2418–2437.
46. May M, Sterne J, Egger M. Parametric survival models may be more accurate than Kaplan-Meier estimates. *BMJ*. 2003;326:822.
47. Gray J, Sullivan T, Latimer NR, et al. Extrapolation of survival curves using standard parametric models and flexible parametric spline models: comparisons in large registry cohorts with advanced cancer. *Med Decis Making*. 2021;41:179–193.
48. Cooper M, Smith S, Williams T, Aguiar-Ibáñez R. How accurate are the longer-term projections of overall survival for cancer immunotherapy for standard versus more flexible parametric extrapolation methods? *J Med Econ*. 2022;25:260–273.
49. Fiala O, Pesek M, Finek J, Benesova L, Bortlicek Z, Minarik M. Comparison of EGFR-TKI and chemotherapy in the first-line treatment of advanced EGFR mutation-positive NSCLC. *Neoplasma*. 2013;60:425–431.