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COST-EFFECTIVENESS ANALYSIS OF ADJUVANT OSIMERTINIB IN RESECTED EGFR-MUTATED EARLY-STAGE NON-SMALL CELL LUNG CANCER IN THAILAND

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Abstract: Lung cancer is the most common cancer and the leading cause of cancer death worldwide. One-third of non-small cell lung cancer (NSCLC) patients are diagnosed in resectable stage, for which curative surgery is the cornerstone of treatment. Adjuvant osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI), was shown to significantly reduce recurrence and prolong survival for completely resected EGFR-mutated NSCLC. We performed a cost-effectiveness analysis of adjuvant osimertinib compared to placebo in patients with resected stage IB to IIIA EGFR-mutated NSCLC using Thailand's societal perspective. A Markov model estimated the lifetime costs and health benefits of osimertinib versus placebo, including three health states: disease-free, recurrent disease, and death, tracked over a lifetime using 4-week cycles. Results were reported as 2023 USD incremental cost-effectiveness ratios (ICERs) per quality-adjusted life year (QALY) gained. The result showed that a virtual patient receiving osimertinib had 2.36 more QALYs than one receiving the placebo, at an incremental cost of 62,604.90 USD. Compared to the placebo group, treatment with adjuvant osimertinib had an ICER of 26,474.02 USD/QALY gained. Therefore, osimertinib was not cost-effective at the Thai willingness-to-pay (WTP) threshold of 4,619 USD/QALY gained. The drug price would need to be reduced by at least 85.07% for osimertinib to be cost-effective. In summary, adjuvant osimertinib for resected EGFR-mutated NSCLC patients is not cost-effective according to Thailand's current WTP threshold. Negotiating drug costs and managed entry agreements could improve patient access to this effective treatment.

Keywords: non-small cell lung cancer, osimertinib, cost-effectiveness, epidermal growth factor receptor, adjuvant therapy

Introduction

Cancer constitutes a significant cause of mortality in Thailand, with lung cancer emerging as a prevalent concern due to its escalating incidence and prevalence over the years. The rise in lung cancer cases, as reported in lung cancer in Thailand study (Reungwetwattana et al., 2020), underscores the pressing nature of this health issue. Concurrently, the 5-year prevalence of lung cancer escalated, with an estimated 31,088 individuals living with the condition in 2022 (World Health Organization, 2022).

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Consequently, the increasing incidence and prevalence of lung cancer in Thailand signify a growing health challenge within the nation.

One-third of non-small cell lung cancer (NSCLC) patients are diagnosed in resectable stage, for which curative surgery is the cornerstone of treatment. However, post-surgical recurrence rates and mortality remain considerable, highlighting the need for more effective interventions. Notably, East and Southeast Asian populations found the prevalence of the epidermal growth factor receptor (EGFR) gene mutation, which paved the way for targeted treatment such as EGFR tyrosine kinase inhibitors (TKIs) (Sukauichai et al., 2022). Osimertinib is a third-generation irreversible EGFR TKI that has demonstrated efficacy in early-stage NSCLC, as evidenced by the ADAURA trials.

The ADAURA trial, phase III RCT, investigated osimertinib adjuvant therapy compared to placebo in patients who have EGFR-mutated resected in stage IB to IIIA NSCLC. Results showed a substantial prolongation of disease-free survival with osimertinib. Moreover, a 5-year overall survival study revealed a significant survival benefit with osimertinib. This was indicated by a hazard ratio for death of 0.49 (95.03% CI, 0.34 to 0.70), highlighting its positive impact on long-term survival outcomes in individuals with EGFR-mutated resected early-stage NSCLC (Herbst et al., 2023; Tsuboi et al., 2023; Wu et al., 2020).

The outcome of the cost-effectiveness analysis of adjuvant osimertinib for patients with completely resected NSCLC and EGFR mutations varies across countries, demonstrating instances of both cost-effectiveness and non-cost-effectiveness when compared to a placebo (Lemmon et al., 2022; Verhoek et al., 2023; Vila Pérez et al., 2023; Zhou et al., 2022). Assessing the cost-effectiveness of adjuvant osimertinib versus placebo for treating EGFR mutations in NSCLC with a complete resection holds significance for health economic decision-making. Insights from this study can inform health economics committees, potentially influencing the addition of osimertinib to the National List of Essential Medicines (NLEM) in Thailand, thus improving access for early-stage NSCLC patients. Despite its high costs, Osimertinib's demonstrated efficacy in preventing disease recurrence and improving overall survival in EGFR-mutated completely resected non-squamous NSCLC (Stage IB to IIIA) underscores its relevance for inclusion in the NLEM. Additionally, the findings of the cost-effectiveness analysis can aid in strategic healthcare budget allocation, particularly given the rising incidence and prevalence of lung cancer in Thailand. While several nations have examined the cost-effectiveness of osimertinib in early-stage NSCLC, Thailand lacks similar research on its utility for completely resected NSCLC with EGFR mutations, making this investigation crucial.

Therefore, the objective of this study is to conduct a cost-effectiveness analysis of adjuvant osimertinib compared to a placebo in patients with resected stage IB to IIIA EGFR-mutated NSCLC, from Thailand’s societal perspective. Additionally, this study differs from those conducted in other countries, as the Markov model was developed in collaboration with lung oncology specialists from a Thai university hospital, ensuring alignment with clinical practice for the treatment of NSCLC in the Thai population. The model also incorporates the timeline of disease recurrence, considering both local/regional recurrence and distant recurrence, wherein patients receive distinct treatments during the progression phase. Furthermore, this study addresses a critical gap by providing significant insights into the economic evaluation of osimertinib, specifically for the Thai population undergoing treatment for

completely resected NSCLC with EGFR mutations, from the perspective of Thai society. These findings can also serve as valuable information for health policymakers.

Materials and Methods

General Overview

The study employed a cost-effectiveness analysis (CEA) to determine the costs and health outcomes of osimertinib in comparison to a placebo by using model-based economic evaluation for patients who complete tumor resection, confirmed EGFR mutation, and WHO performance status of 0 or 1 with primary nonsquamous non-small cell lung cancer with stage IB, II, or IIIA. The determination was the patient aged 18 years or older, and those who had already had adjuvant chemotherapy or were unable to receive platinum-based chemotherapy followed the population in the ADUARA trial. The model treatment pathway encompasses two arms: the osimertinib arm and the placebo arm, depicted in Figure 1. In the disease-free survival (DFS) stage, patients were administered either osimertinib 80 mg per day (maximum 3 years) or placebo. In the event of recurrent disease (RD), patients could experience either a local-regional or distant recurrence. Noteably, patients in the osimertinib arm who experienced recurrence within 3 years received subsequent treatment within the osimertinib arm. However, those who experienced recurrence after 3 years received subsequent treatment identical to that in the placebo arm.

This treatment pathway adheres to clinical practice guidelines for lung cancer treatment in Thailand (The National Cancer Institute Library, 2015), as well as the National Comprehensive Cancer Network guideline (National Comprehensive Cancer Network, 2024), European Society for Medical Oncology guideline (Hendriks et al., 2023), and expert opinions.

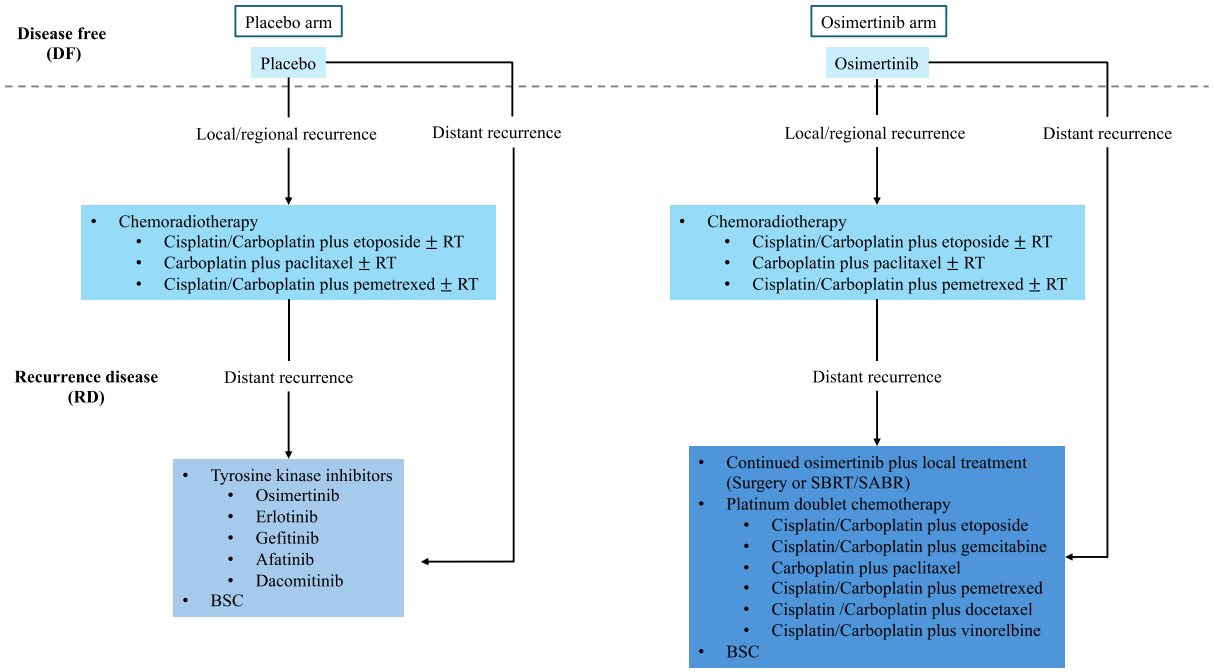

Figure 1: Treatment pathway

Model Structure

The study employed a comprehensive economic evaluation employing Markov models, which were developed from the perspective of Thai society in accordance with the Thai health technology assessment guidelines (Guideline Development Working Group, 2019). These models were tailored to project outcomes and costs related to the treatment of resected early-stage NSCLC in patients with EGFR mutations. The constructed model underwent validation by lung oncologists and health economists.

The Markov model comprised three distinct health states: disease-free survival (DFS), recurrence disease (RD), and death, as illustrated in Figure 2. Initially, patients were in the DFS state and then moved to other health states, such as RD or death, or remained in the same state for the subsequent cycle. The modeling process continued until the entire population reached the state of death, which served as an absorbing health state. Patient trajectories were tracked over their lifetime horizon using a 4-week cycle. The model assumes that once patients progress to the RD state, they cannot revert to being disease-free.

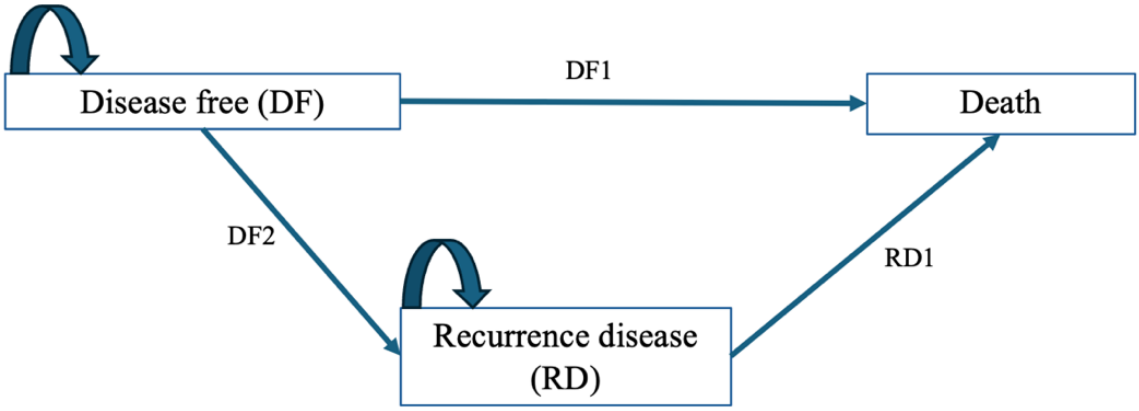

Figure 2: Markov model of stage IB-IIIA NSCLC

Input Parameters

The model input parameters consist of a range of variables, including the transition probability shifts between health states, costs, and utility data. These parameters are analyzed to derive metrics for the outcome of quality-adjusted life years (QALYs) and costs. Furthermore, the results were exposed to a 3% discount rate. The specific information regarding the model input parameter can be found in Appendix Table 1S.

Transition probability data

The transitions from the DF health state were informed by data from the updated ADAURA trial. However, as the ADAURA trial lacked data on transitions out of the RD state, supplemental information was sourced from other trials. Therefore, the transition out of the RD state is derived from the trials that involved the drug receiving subsequent treatment, such as the FLAURA trial (Ramalingam et al., 2019),

the LAURA trial (Ramalingam et al., 2024), the PACIFIC trial (Spigel et al., 2022), a study by (Mok et al., 2009), and a study by (Shepherd et al., 2000). Additionally, the transition probability was also calculated with the proportion of the alternative of using subsequent treatment in NSCLC Thai patients, which collected data from interview specialists in lung oncology from three hospital universities in Thailand.

Furthermore, the disease-specific mortality rate (μ_D) for NSCLC was calculated from the deaths of NSCLC and other causes. The mortality rates for NSCLC were derived from existing literature, and the age-specific mortality rates for the general population in Thailand were sourced from statistics provided by the Ministry of Public Health in Thailand. (Ministry of Public Health, 2022) The equation for calculation was shown as follows:

$$\mu_D = \mu_C - \mu_{ASMR}$$

In this equation, μ_D represents the disease-specific mortality rate for NSCLC, μ_C refers to overall mortality rate of NSCLC obtained from literatures, and μ_ASMR refers the age-, sex-, and race-specific mortality rate from the Ministry of public health in Thailand (Ministry of Public Health, 2022). The methodology for calculated the disease-specific mortality rate derived from (Thaweethamcharoen et al., 2014).

Cost data

In our analysis of Thai society, we examined direct medical costs, direct non-medical costs, and indirect costs. The Thai Consumer Price Index (CPI) was utilized to adjust for inflation, with subsequent conversion to USD based on the 2023 exchange rate of 34.6394 THB per USD (BANK OF THAILAND, 2023). All costs were derived from various sources and were discounted annually at a rate of 3%, in accordance with the guidelines specified in the Thailand Health Technology Assessment Guideline (Guideline Development Working Group, 2019).

The drug acquisition costs for osimertinib were obtained from primary data from Siriraj Hospital. Subsequent treatment costs pertain to the expenditures incurred subsequent to patients experiencing disease recurrence in either the local/regional recurrence or distant recurrence health states. The costs for subsequent treatment drugs were obtained from the website of the Drug and Medical Supply Information Center in Thailand (Drug And Medical Supply Information Center, 2023). The determination of subsequent treatment proportions was guided by specialist lung oncologists.

The cost of thoracotomy with resection of thoracic tumors was obtained from the standard cost list for health technology assessment (Riewpaiboon, 2009). The costs related to visits with specialized physicians, nursing services, drug dispensation, radiotherapy, and mixed chemotherapy were calculated based on the median frequency of patient follow-up visits, as recommended by four specialist lung oncologists. These costs were also derived from the standard cost list for health technology assessment (Riewpaiboon, 2009).

Laboratory test costs, including the EGFR mutation test administered once to confirm EGFR mutation status prior to osimertinib or placebo administration, were obtained from the Siriraj Hospital website. The costs for additional tests such as computerized tomography (CT) of the lung, X-rays, creatinine

tests, EKG, liver function tests, blood urea nitrogen, electrolytes, and a complete blood count were derived from the standard cost list for health technology assessment (Riewpaiboon, 2009) and calculated based on the median follow-up frequency recommended by four specialist lung oncologists.

The cost of adverse events (AEs) was determined through an analysis of the percentage of AEs associated with osimertinib or placebo, as reported in the ADAURA trial (Herbst et al., 2023). This analysis specifically focused on the most prevalent AEs documented in clinical trials, occurring in ≥ 10% of patients within the osimertinib or placebo treatment cohorts. Furthermore, the study accounted for the expenses linked to treating severe adverse events, such as pneumonia. The costs related to treating Adverse Events (AEs) were calculated by multiplying the percentage of each occurrence by its corresponding cost per unit, as specified in Table 1. The cost estimations for AEs were obtained through a comprehensive review of the literature (Permsuwan et al., 2014; Riewpaiboon et al., 2020).

Direct non-medical costs encompass costs related to patient and caregiver transportation to the hospital, as well as the costs associated with food for both the patient and caregiver. These costs were sourced from the standard cost list of HITAP for health technology assessment (Riewpaiboon, 2009).

Indirect costs include the duration of time spent by caregivers accompanying patients to hospital appointments for follow-up visits or during treatments such as osimertinib or placebo. These costs were obtained from the standard cost list for health technology assessment (Riewpaiboon, 2009). To determine the cost of caregiver time, the total number of caregiver days lost was multiplied by the average earnings per day, following recommendations from the Thai health technology assessment guidelines (Guideline Development Working Group, 2019).

Table1: The proportion of adverse events

Adverse events	**Osimertinib**	**Placebo**
Diarrhea	40%	14%
Paronychia	25%	1%
Dry skin	22%	5%
Pruritus	18%	7%
Rash/Stomatitis	16%	2%
Dermatitis acneiform	11%	3%
Pneumonia	1%	1%

Utility data

We adopted utility data for the DF state from the average of four studies on the CEA of osimertinib in early-stage resected NSCLC with EGFR-positive patients in other countries (Lemmon et al., 2022; Verhoek et al., 2023; Vila Pérez et al., 2023; Zhou et al., 2022). This method was necessary as there was a limitation of utility data for Thai individuals receiving osimertinib treatment for this specific disease.

We did not acquire Health-Related Quality of Life (HRQoL) data from the ADAURA trial since the trial assessed HRQoL using the Short Form-36 (SF-36) health survey. In accordance with the Health Technology Assessment (HTA) guidelines in Thailand, the recommended instrument for the Thai population is the European Quality-of-Life, 5-Dimension (EQ-5D) questionnaire.

The utility values for patients who received chemoradiotherapy for local/regional recurrent disease were derived from a study conducted by (Grutters et al., 2010). The utility values associated with the distant recurrence disease state were derived from the study conducted by (Limwattananon et al., 2018). This research gathered utility values specific to the Thai population utilizing the EQ-5D questionnaire. The purpose was to evaluate the CEA of TKIs as first-line treatments for patients diagnosed with advanced NSCLC in Thailand.

Additionally, the utility value for best supportive care in patients with distant recurrent disease was obtained from the study by (Kangwanrattanakul, 2022), which gathered utility data on best supportive care for Thai patients with stage IIIA, IIIB, and IV NSCLC.

Cost-effectiveness analysis

Base Case Analysis

In the base case analysis, we conducted a comparison of the total lifetime costs, life years, and QALYs among patients with EGFR-mutated early-stage NSCLC who received adjuvant treatment with osimertinib versus placebo. Subsequently, the incremental cost-effectiveness ratio (ICER) was calculated accordingly. To evaluate the cost-effectiveness of the intervention, we applied the local ICER threshold in Thailand, set at $4,619 per QALY gained (160,000 THB per QALY gained).(Guideline Development Working Group, 2019)

Results and Discussion

Base case analysis

From the base case analysis, it was determined that osimertinib therapy provided a total of 8.22 QALYs and a life expectancy of 10.33 years. In comparison, the placebo group accrued 5.86 QALYs and a life expectancy of 7.52 years. Thus, patients receiving osimertinib experienced an additional 2.36 QALYs and 2.81 years of life expectancy compared to those receiving placebo. The lifetime cost of osimertinib treatment per patient amounted to $71,801.64 (2,487,165.81 THB), whereas the placebo treatment incurred a total cost of $9,196.74 (318,569.69 THB). Consequently, the incremental cost associated with osimertinib therapy was $62,604.90 (2,168,596.12 THB). This results in an ICER of $26,474.02 per QALY gained when compared to the placebo. However, given the willingness-to-pay (WTP) threshold in Thailand of $4,619 per QALY gained (160,000 THB per QALY gained), osimertinib did not meet the criteria for cost-effectiveness. To achieve cost-effectiveness within this threshold, the price of osimertinib would need to be reduced by at least 85.07%. Table 2 provides particular data.

Table 2: Lifetime cost and health outcomes of resected stage IB to IIIA EGFR-mutated NSCLC.

Treatment option	Total cost (USD)	LYs	QALYs	Incremental cost (USD)	Incremental QALYs	ICERs (USD/QALY gained)
Placebo	9,196.74	7.52	5.86	-	-	-
Osimertinib	71,801.64	10.33	8.22	62,604.90	2.36	26,474.02

USD, US dollars; LYs, Life years; QALYs, quality-adjusted life years; ICERs, incremental cost-effectiveness ratios

Based on the ICER results, osimertinib is not cost-effective for Thai patients with early-stage EGFR-mutated NSCLC. Therefore, to improve cost-effectiveness, the price of osimertinib must be reduced. Strategies such as those previously implemented in Thailand, including price negotiations, or the application of managed entry agreements (MEAs), could be utilized. These approaches can help Thai patients access the benefits of this drug for the treatment of NSCLC.

Discussion

Patients with early-stage NSCLC harboring EGFR mutations are at high risk of disease recurrence following tumor resection. Even with adjuvant chemotherapy, the risk of recurrence remains significant. Osimertinib has demonstrated efficacy for increasing disease-free survival and prolonging overall survival in the ADAURA trial. However, the high cost of osimertinib, at $1,963.37 per month, necessitates an economic evaluation to assess its cost-effectiveness.

This study represents the first economic evaluation of osimertinib treatment for early-stage NSCLC in Thailand. Our results indicate that osimertinib provides an additional 2.36 QALYs and extends life expectancy by 2.81 years. However, it incurs an incremental cost of $62,604.90, resulting in an ICER of $26,474.02 per QALY gained, and the probability of osimertinib being cost-effective is 0% at the current Thai WTP threshold, necessitating an 85.07% price reduction to achieve cost-effectiveness.

Our findings align with previous cost-effectiveness studies of osimertinib in the same indication conducted in (Lemmon et al., 2022) and (Vila Pérez et al., 2023), both of which concluded that osimertinib, despite providing higher QALYs than placebo, is not cost-effective under their respective WTP thresholds without significant price reductions. Conversely, studies from (Zhou et al., 2022) and (Verhoek et al., 2023) found osimertinib to be cost-effective within their WTP thresholds.

However, our study differs from other economic evaluations of osimertinib treatment for early-stage NSCLC in several key aspects. Notably, we considered the timeline of recurrent disease, distinguishing between patients who experience recurrence within three years and those who recur after three years, as these groups receive different subsequent treatments. Furthermore, our study utilized updated five-year overall survival data from the ADAURA trial to calculate the transition probabilities to death for patients receiving osimertinib or placebo in the disease-free state. In contrast, other studies have used transition probabilities to death derived from the FLAURA trial, which assessed the efficacy of osimertinib in metastatic NSCLC patients.

In this analysis, the Markov model utilized three primary states. The recurrence state was further divided into local/regional recurrence and distant recurrence to comprehensively capture all clinical outcomes in patients after resection and adjuvant treatment for NSCLC. The model employed a lifetime horizon to track outcomes until all patients had died.

This study has several notable strengths. First, the model incorporated data on the proportions of subsequent treatments for local/regional and distant recurrence from specialists at three university hospitals in Thailand, ensuring the results reflect real-world clinical practice in Thailand. Second, the model considered the timeline of disease recurrence, with different treatments for recurrences within and beyond three years, following specialist recommendations. Third, the mortality rates were adjusted using age-specific mortality data for the Thai population, enhancing the relevance for local policymakers. Finally, input parameters and model were validated by lung oncologists and health economists, ensuring the robustness of our cost-effectiveness analyse.

However, there are limitations. The efficacy data for osimertinib were based solely on the ADAURA trial, as real-world evidence is still limited. Future studies incorporating more real-world data will be essential for validating these findings. Furthermore, while the model used five-year survival data without extrapolation to minimize bias, this approach might underrepresent long-term benefits. Utility values were sourced from international studies rather than direct patient data from the ADAURA trial, as the SF-36 questionnaire used in ADAURA is less suitable for the Thai population. Future research should address these limitations. If real-world evidence specific to the Thai population or primary data on costs and utility values in the Thai context become available, it would enhance the accuracy of the ICER results for Thailand.

Finally, while our study emphasizes the need to enhance cost-effectiveness and patient access, drug price negotiations and managed entry agreements (MEAs) are identified as crucial strategies. Drug price negotiations have previously proven successful in Thailand, as demonstrated by the reduction in the price of erlotinib for the treatment of advanced-stage EGFR-mutated NSCLC in Thai patients. Additionally, MEAs have emerged as a contemporary approach, involving arrangements between pharmaceutical companies and healthcare payers to manage the introduction of new drugs under conditions of uncertainty. These agreements may include outcome-based pricing, where the drug's price is linked to the health outcomes it delivers, or financial-based arrangements such as discounts, rebates, or price-volume agreements. By implementing MEAs, the financial burden on the healthcare system can potentially be reduced, making osimertinib more affordable and accessible to patients.

Conclusion

Adjuvant osimertinib for patients with resected EGFR-mutated NSCLC is not cost-effective under Thailand’s current willingness-to-pay (WTP) threshold. The high drug cost significantly impacts the incremental cost-effectiveness ratio (ICER), making it a critical factor in the overall economic evaluation. Consequently, osimertinib's high price poses a substantial barrier to its cost-effectiveness despite its clinical benefits. To improve cost-effectiveness and patient access, drug cost negotiations and managed entry agreements (MEAs) are essential strategies. These approaches can potentially reduce the financial burden, making osimertinib more affordable. Nevertheless, the ICER results in this

study have certain limitations, including the lack of real-world evidence and the use of utility values derived from international studies, which may not accurately reflect the ICER outcomes within the Thai population.

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Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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Appendix

Table 1S: The model input parameters

Input Parameter	Distribution	Base case values	Max	Min	Reference
Transition probabilities (4 weeks)					
Disease-free to recurrence					
Placebo arm					
DF to local RD chemoradiotherapy	Beta	0.0044	0.0055	0.0033	(Herbst et al., 2023)

DF to distant RD Osimertinib	Beta	0.0011	0.0013	0.0008	(Herbst et al., 2023)
DF to distant RD TKIs	Beta	0.0057	0.0071	0.0042	(Herbst et al., 2023)
DF to distant RD BSC	Beta	0.0004	0.0004	0.0003	(Herbst et al., 2023)
Osimertinib arm					
Recurrent within 3 years					
DF to local RD chemoradiotherapy	Beta	0.0023	0.0029	0.0017	(Herbst et al., 2023)
DF to distant RD Osimertinib plus local treatment	Beta	0.0002	0.0003	0.0002	(Herbst et al., 2023)
DF to distant RD PDC	Beta	0.0025	0.0032	0.0019	(Herbst et al., 2023)
DF to distant RD BSC	Beta	0.0001	0.0001	0.0001	(Herbst et al., 2023)
Recurrent after 3 years					
DF to local RD chemoradiotherapy	Beta	0.0023	0.0029	0.0017	(Herbst et al., 2023)
DF to distant RD Osimertinib	Beta	0.0004	0.0005	0.0003	(Herbst et al., 2023)
DF to distant RD TKIs	Beta	0.0023	0.0029	0.0017	(Herbst et al., 2023)
DF to distant RD BSC	Beta	0.0001	0.0002	0.0001	(Herbst et al., 2023)

Disease-free to Death					
Placebo arm					
DF to death	Beta	0.0025	0.0031	0.0019	(Tsuboi et al., 2023)
Osimertinib arm					
DF to death	Beta	0.0013	0.0017	0.0010	(Tsuboi et al., 2023)
Local/regional recurrence to death					
Placebo arm					
Local RD Chemoradiotherapy to death	Beta	0.0130	0.0163	0.0098	(Ramalingam et al., 2024)
Osimertinib arm					
Recurrent within 3 years					
Local RD Chemoradiotherapy to death	Beta	0.0130	0.0163	0.0098	(Ramalingam et al., 2024)
Recurrent after 3 years					
Local RD Chemoradiotherapy to death	Beta	0.0130	0.0163	0.0098	(Ramalingam et al., 2024)
Distant recurrence to death					
Placebo arm					
Distant RD Osimertinib to death	Beta	0.0153	0.0192	0.0115	(Ramalingam et al., 2019)
Distant RD TKIs to death	Beta	0.0193	0.0242	0.0145	(Ramalingam et al., 2019)

Distant RD BSC to death	Beta	0.1199	0.1498	0.0899	(Shepherd et al., 2000)
Osimertinib arm					
Recurrent within 3 years					
Distant RD Osimertinib plus local treatment to death	Beta	0.0153	0.0192	0.0115	(Ramalingam et al., 2019)
Distant RD PDC to death	Beta	0.0404	0.0505	0.0303	(Mok et al., 2009)
Distant RD BSC to death	Beta	0.1199	0.1498	0.0899	(Shepherd et al., 2000)
Recurrent after 3 years					
Distant RD Osimertinib to death	Beta	0.0153	0.0192	0.0115	(Ramalingam et al., 2019)
Distant RD TKIs to death	Beta	0.0193	0.0242	0.0145	(Ramalingam et al., 2019)
Distant RD BSC to death	Beta	0.1199	0.1498	0.0899	(Shepherd et al., 2000)
Local/regional recurrence to distant recurrence					
Placebo arm					
Local RD chemoradiotherapy to Distant RD Osimertinib	Beta	0.0084	0.0105	0.0063	(Spigel et al., 2022)

Local RD chemoradiotherapy to Distant RD TKIs	Beta	0.0449	0.0562	0.0337	(Spigel et al., 2022)
Local RD chemoradiotherapy to Distant RD BSC	Beta	0.0028	0.0035	0.0021	(Spigel et al., 2022)
Osimertinib arm					
Recurrent within 3 years					
Local RD chemoradiotherapy to Distant RD PDC	Beta	0.0538	0.0673	0.0404	(Spigel et al., 2022)
Local RD chemoradiotherapy to Distant RD BSC	Beta	0.0023	0.0028	0.0017	(Spigel et al., 2022)
Recurrent after 3 years					
Local RD chemoradiotherapy to Distant RD Osimertinib	Beta	0.0084	0.0105	0.0063	(Spigel et al., 2022)
Local RD chemoradiotherapy to Distant RD TKIs	Beta	0.0449	0.0562	0.0337	(Spigel et al., 2022)
Local RD chemoradiotherapy to Distant RD BSC	Beta	0.0028	0.0035	0.0021	(Spigel et al., 2022)
Cost					

Direct medical costs					
Drug acquisition cost (2023; USD per dosage unit)					
Osimertinib 80 mg (30 TAB)	Gamma	1963.37	2454.21	1472.53	Primary data
Subsequent drug cost (2023; USD per dosage unit)					
Osimertinib arm (All cycle treatment)					
Recurrent within 3 years					
chemoradiotherapy	Gamma	816.77	1020.96	612.58	(Drug And Medical Supply Information Center, 2023), (Riewpaiboon, 2009)
Continute osimertinib+local	Gamma	3063.45	3829.31	2297.59	Primary data
Platinum doublet chemotherapy	Gamma	1708.70	2135.87	1281.52	(Drug And Medical Supply Information Center, 2023)
BSC	Gamma	34.87	43.58	26.15	(Limwattananon et al., 2018)
Recurrent after 3 years					
chemoradiotherapy	Gamma	816.77	1020.96	612.58	(Drug And Medical Supply Information Center, 2023)
Osimertinib	Gamma	6065.94	7582.42	4549.45	Primary data
TKIs	Gamma	1565.85	1957.32	1174.39	(Drug And Medical Supply Information Center, 2023)

BSC	Gamma	43.15	53.94	32.36	(Limwattananon et al., 2018)
Placebo arm (All cycle treatment)					
chemoradiotherapy	Gamma	816.77	1020.96	612.58	(Drug And Medical Supply Information Center, 2023)
Osimertinib	Gamma	6065.94	7582.42	4549.45	Primary data
TKIs	Gamma	1244.29	1555.36	933.22	(Drug And Medical Supply Information Center, 2023)
BSC	Gamma	43.15	53.94	32.36	(Limwattananon et al., 2018)
Administration cost (2023; USD per time)					
Cost of thoracotomy with resection of thoracic tumor	Gamma	265.26	331.57	198.94	(Riewpaiboon, 2009)
Cost of specialist physician	Gamma	9.15	11.44	6.86	(Riewpaiboon, 2009)
Cost of nurse	Gamma	2.17	2.71	1.62	(Riewpaiboon, 2009)
Cost of dispending drugs	Gamma	2.20	2.75	1.65	(Riewpaiboon, 2009)
Cost of radiotherapy	Gamma	38.79	48.49	29.10	(Riewpaiboon, 2009)
Cost of mixed chemotherapy	Gamma	6.98	8.73	5.24	(Riewpaiboon, 2009)

Laboratory test costs (2023; USD per time)					
EGFR mutation test	Gamma	213.92	267.40	160.44	(Siriraj hospital, 2023)
computerized tomography lung	Gamma	218.15	272.69	163.62	(Riewpaiboon, 2009)
X-ray	Gamma	7.40	9.25	5.55	(Riewpaiboon, 2009)
CBC	Gamma	3.91	4.89	2.93	(Riewpaiboon, 2009)
Electrolyte	Gamma	3.49	4.36	2.62	(Riewpaiboon, 2009)
Blood Urea Nitrogen	Gamma	2.17	2.71	1.62	(Riewpaiboon, 2009)
Liver function test	Gamma	15.26	19.07	11.44	(Riewpaiboon, 2009)
EKG	Gamma	13.09	16.37	9.82	(Riewpaiboon, 2009)
Creatinine	Gamma	2.17	2.71	1.62	(Riewpaiboon, 2009)
Adverse event costs (2023; USD per treatment)					
Diarrhea	Gamma	4.51	5.63	3.38	(Permsuwan et al., 2014)
Paronychia	Gamma	5.57	6.96	4.18	(Permsuwan et al., 2014)
Dry skin	Gamma	2.50	3.13	1.88	(Permsuwan et al., 2014)
Pruritis	Gamma	4.69	5.87	3.52	(Permsuwan et al., 2014)
Rash/stomatitis	Gamma	4.69	5.87	3.52	(Permsuwan et al., 2014)
Dermatitis acneiform	Gamma	4.69	5.87	3.52	(Permsuwan et al., 2014)

Pneumonitis	Gamma	260.91	326.14	195.69	(Reechaipichitkul et al., 2014)
Direct non-medical costs (2023; USD per time)					
Cost of transportation to hospital of patient	Gamma	4.61	5.76	3.46	(Riewpaiboon, 2009)
Cost of transportation to hospital of caregiver	Gamma	4.61	5.76	3.46	(Riewpaiboon, 2009)
Cost of food of patient	Gamma	1.70	2.12	1.27	(Riewpaiboon, 2009)
Cost of food of caregiver	Gamma	1.70	2.12	1.27	(Riewpaiboon, 2009)
Indirect costs (2023; USD per time)					
Cost of productivity loss of caregiver	Gamma	5.88	7.35	4.41	(Riewpaiboon, 2009)
Utility					
Placebo arm					
diseas-free survival state					
Placebo	Beta	0.83	1.0	0.62	(Zhou et al., 2022), (Verhoek et al., 2023), (Lemmon et al., 2022), (Vila Pérez et al., 2023)

local/regional recurrence state					
Chemoradiotherapy	Beta	0.76	0.95	0.57	(Grutters et al., 2010)
Distant recurrence state					
Osimertinib	Beta	0.67	0.84	0.50	(Limwattananon et al., 2018)
TKIs	Beta	0.67	0.83	0.50	(Limwattananon et al., 2018)
BSC	Beta	0.27	0.34	0.20	(Kangwanrattanakul, 2022)
Osimertinib arm					
diseas-free survival state					
Osimertinib	Beta	0.82	1.00	0.62	(Zhou et al., 2022), (Verhoek et al., 2023), (Lemmon et al., 2022), (Vila Pérez et al., 2023)
local/regional recurrence state					
Chemoradiotherapy	Beta	0.76	0.95	0.57	(Grutters et al., 2010)
Distant recurrence state (Before 3 year recurrence)					
Osimertinib+local	Beta	0.67	0.84	0.50	(Limwattananon et al., 2018)
Platinum doublet chemotherapy	Beta	0.54	0.68	0.41	(Limwattananon et al., 2018)
BSC	Beta	0.27	0.34	0.20	(Kangwanrattanakul, 2022)
Distant recurrence state (After 3 year recurrence)					

Osimertinib	Beta	0.67	0.84	0.50	(Limwattananon et al., 2018)
TKIs	Beta	0.67	0.84	0.50	(Limwattananon et al., 2018)
BSC	Beta	0.27	0.34	0.20	(Kangwanrattanakul, 2022)

DF, Disease-free; RD, Recurrence disease; TKIs, Tyrosine kinase inhibitors; BSC, best supportive care; PDC, platinum doublet chemotherapy; CBC, Complete Blood Count; EGFR, Epidermal Growth Factor Receptor