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Cost-utility and budget impact analyses of anaplastic lymphoma kinase inhibitors in Thailand

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Second-generation anaplastic lymphoma kinase (ALK) inhibitors, including ceritinib, brigatinib, and alectinib, have improved survival in ALK-rearranged non-small-cell lung cancer (NSCLC) but are not included in Thailand's National List of Essential Medicines. This study assessed the cost-utility and budget impact of second-generation ALK inhibitors compared to chemotherapy for advanced NSCLC in Thailand. A Markov model was employed to estimate costs and quality-adjusted life years (QALYs) from a societal perspective. Cost data were derived from the Thai Health Technology Assessment Database, published literature, and clinical guidelines. Health-related quality of life (HRQoL) was assessed using EQ-5D-5L, and transitional probabilities were extracted from published studies. Incremental cost-effectiveness ratios (ICERs) and sensitivity analyses were conducted. A five-year budget impact analysis (BIA) was performed from the payer's perspective. Our analysis shows that chemotherapy remained the most cost-effective option. Although all ALK inhibitors yielded higher QALYs, the lifetime costs associated with their use cannot be offset by the additional outcomes gained. This was primarily due to Thailand's willingness-to-pay threshold, which was lower than the ICERs of all ALK inhibitors. Sensitivity analyses confirmed that none of the ALK inhibitors were cost-effective compared to chemotherapy. The five-year BIA estimated the budget impact of ceritinib (450 mg/day, 750 mg/day), alectinib (600 mg/day, 1,200 mg/day), and brigatinib at 2,345 (63.81), 3,703 (100.76), 9,830 (267.49), 19,328 (525.92), and 9,502 (258.56) million THB (USD), respectively.

Keywords Cost-utility analysis, Non-small cell lung cancer, Ceritinib, Brigatinib, Alectinib

Lung cancer is one of the top five most common cancers in Thailand, with a five-year prevalence rate of 36.05 per 100,000 population[1]. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases[2]. Despite advances in treatment, NSCLC is a biologically heterogeneous disease characterized by multiple oncogenic drivers that influence both prognosis and therapeutic options[3].

Among these drivers, epidermal growth factor receptor (EGFR) mutations are particularly prevalent in Asian populations, occurring in approximately 30–50% of NSCLC cases, and are associated with favorable responses to EGFR tyrosine kinase inhibitors (TKIs)[4,5]. In Western populations, KRAS mutations are found in approximately 25–30% of NSCLC (especially adenocarcinomas)[6,7] and are generally associated with a poorer prognosis and limited targeted treatment options[8]. Anaplastic lymphoma kinase (ALK) rearrangements, although present in only 3–5% of NSCLC cases[9], confer substantial clinical benefits when treated with ALK-targeted therapies[10]. These molecular distinctions underscore the importance of specifically evaluating ALK-positive NSCLC in Thailand, where mutation prevalence, treatment practices, and access barriers differ significantly from those in high-income countries[11–13].

The National Comprehensive Cancer Network (NCCN) recommends ALK inhibitors as the standard first-line therapy for advanced or metastatic ALK-positive NSCLC[14]. Several randomized phase III trials have demonstrated that second-generation ALK inhibitors significantly improve clinical outcomes compared with the first-generation inhibitor crizotinib. The ALTA-1 L trial showed that brigatinib provided superior PFS versus crizotinib, with a particularly pronounced benefit in Asian patients (HR 0.35, 95% CI 0.20–0.59; median 24.0 vs.

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11.1 months)[15]. The ASCEND-4 trial further demonstrated that the second-generation ALK inhibitor ceritinib significantly improved PFS compared with platinum-based chemotherapy (HR 0.55, 95% CI 0.42–0.73; median 16.6 vs. 8.1 months)[16]. These trials showed the clinical superiority of next-generation ALK inhibitors over both crizotinib and chemotherapy, particularly in terms of PFS.

In Thailand, platinum-based chemotherapy remains the standard of care under the Universal Coverage Scheme (UCS)[17]. Patients with stage IIIB–IV NSCLC are typically treated with platinum-doublet chemotherapy regimens, such as carboplatin plus paclitaxel, gemcitabine plus cisplatin, or gemcitabine plus carboplatin[17] which is reimbursed under Thailand's major public health insurance scheme. Pemetrexed plus cisplatin and pemetrexed plus carboplatin are also widely used in clinical practice[18,19] but pemetrexed itself is not reimbursed under the UCS[13]. To ensure accuracy, these practice patterns were validated by clinicians involved in this study and supplemented with published Thai oncology literature[12].

Previous cost-effectiveness analyses (CEAs) of ALK inhibitors in other countries have focused mainly on within-ALK inhibitors comparisons, most commonly evaluating ceritinib, alectinib, brigatinib, or lorlatinib against crizotinib[20–22]. Several of these studies concluded that newer ALK inhibitors could be considered cost-effective under specific healthcare system conditions[23–27]. However, evidence on chemotherapy-based comparators remains limited, particularly in resource-constrained settings where chemotherapy-based regimens still represent the main standard of treatment.

Given the high clinical and economic burden of ALK-positive NSCLC, together with the scarcity of local cost-effectiveness and budget impact evidence, there is an unmet need for economic evaluations to guide reimbursement decisions in Thailand as well as other resource constrained settings. Therefore, this study aims to evaluate the cost-utility and budget impact of ceritinib, brigatinib, and alectinib compared with standard chemotherapy regimens for treating advanced ALK-positive NSCLC using Thailand as a case study.

Methods

Model description

A Markov model was employed to estimate the costs, life years (LYs), and quality-adjusted life years (QALYs) in patients with ALK-positive advanced NSCLC over a lifetime horizon. The model comprised three health states: progression-free disease (PFD), progressive disease (PD), and death (Fig. 1). The analysis was initiated at a starting age of 50 years, reflecting the average age of Thai lung cancer patients[28]. All patients entered the model in the PFD state after receiving an intervention or a comparator as first-line therapy. Patients who progressed to the PD state were administered docetaxel (75 mg/m^2) as second-line therapy for a total of four cycles, followed by best supportive care (BSC) until death. These treatment strategies were aligned with Thai clinical practice guidelines and the National Health Security Office (NHSO) cancer treatment protocol[2,17].

For the base case setting, the model was structured with a three-week cycle and a lifetime horizon, conducted from a societal perspective. Both costs and QALYs were discounted at 3% following the Thai Health Technology Assessment (HTA) guidelines[29]. The exchange rate for converting the Thai baht (THB) to the United States dollar (USD) was set at 36.75 THB per USD, based on the Bank of Thailand exchange rate as of April 18, 2024[30]. Drug wastage was not explicitly modeled, as ALK inhibitors are administered orally at fixed daily doses, and chemotherapy costs were estimated using standard dosing regimens without additional wastage assumptions. The incremental cost-effectiveness ratio (ICER) was calculated to assess cost-utility using a cost-effectiveness threshold of 160,000 THB/QALY (4,353.74 USD/QALY), representing Thailand's willingness-to-pay (WTP) threshold[31].

This study (IRB No. 0642/65) has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. This study complies with the international guidelines for human research protection, including the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines, and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP). Written informed consent was obtained from the subset of patients at King Chulalongkorn Memorial Hospital from whom EQ-5D-5 L utility data were collected. All other analyses were based solely on secondary and published data, for which consent was not applicable.

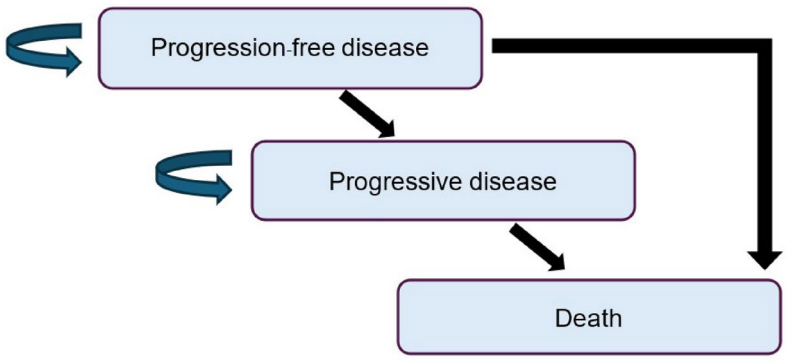

Fig. 1. Markov model

Intervention and comparators

This study compared second-generation ALK inhibitors (ceritinib, brigatinib, and alectinib) with standard chemotherapy regimens. Crizotinib, a first-generation ALK inhibitor, was not included because its efficacy and safety are inferior to second-generation ALK inhibitors. Lorlatinib, a third-generation ALK inhibitor, was not assessed because it had not yet received regulatory approval for use in Thailand during the study period. The standard chemotherapy options included carboplatin plus paclitaxel, gemcitabine plus cisplatin, and gemcitabine plus carboplatin, which are currently reimbursed by the major public health insurance scheme in Thailand. Pemetrexed plus cisplatin and pemetrexed plus carboplatin were also included as comparators, as they are commonly used in real-world clinical practice in Thailand. To estimate chemotherapy dosing, a body surface area (BSA) of 1.6 m^2 was applied, reflecting the average BSA of the Thai population[18]. The dosing regimens for second-generation ALK inhibitors were as follows: ceritinib: 450 mg/day with food or 750 mg/day, brigatinib: 90 mg/day for the first 7 days, then increased to 180 mg/day, and alectinib: 600 mg/day or 1,200 mg/day.

Costs

To reflect the societal perspective, both direct medical costs and direct non-medical costs were included in the analysis. Direct medical costs included the costs of acquiring drugs from the Drug and Medical Supply Information Center (DMSIC)[32]. The cost of medications was last updated in December 2024. BSC costs adopted from a hospital database of prior Thai published research, which included treatment of malignant pleural effusion, palliative radiation, pain control, and nutritional support[18]. The costs of managing adverse events, limited to grades 3 and 4, were based on published studies[33]. The analysis assumed that adverse events occurred independently, with associated costs incurred as a one-time expenditure. To estimate the economic burden, the incidence rates of adverse events derived from pivotal clinical trials were multiplied by the corresponding unit costs from the Thai HTA standard cost lists. Hospital-related medical expenses, including physician fees, nursing services, pharmacy dispensing fees, chemotherapy preparation, and laboratory tests, were derived from the Thai HTA standard cost lists and published literature[18,34]. Administration costs for chemotherapy administered via intravenous infusion were not itemized separately; instead, they were incorporated within the nursing service fees.

Direct non-medical costs, including transportation and additional food expenses, were also derived from the Thai HTA standard cost lists[34]. Resource utilization was aligned with Thai clinical practice guidelines and the NHSO cancer treatment protocol. Indirect costs such as productivity loss were not included, consistent with the Thai HTA guidelines, as QALYs already capture productivity effects[29].

Utilities

Utility values were gathered through a cross-sectional survey at King Chulalongkorn Memorial Hospital using the Thai EQ-5D-5 L questionnaire[35]. The EQ-5D instrument utilized in this study was not obtained from the EuroQol Research Foundation and thus does not strictly correspond to its designated use. Patients were recruited by their physicians and allocated into treatment groups based on current regimens: carboplatin plus paclitaxel ($n = 6$), gemcitabine plus carboplatin ($n = 8$), pemetrexed plus carboplatin ($n = 6$), ceritinib ($n = 9$), alectinib ($n = 8$), docetaxel ($n = 8$), and BSC ($n = 6$). Patients were interviewed face-to-face during routine clinical visits by trained research staff. Since no patients received brigatinib during the study period, its utility was assumed to be comparable to alectinib and supplemented with published literature, with sensitivity analyses conducted for robustness[36,37].

Inclusion criteria were Thai patients aged over 18 years, with histologically confirmed stage IIIB–IV NSCLC, who had received at least one month or three cycles of therapy, were able to communicate in Thai, and provided written informed consent. Exclusion criteria were cognitive impairment, inability to follow up, or withdrawal. Sample size was determined using G*Power ($\alpha = 0.05$, power = 0.80, effect size = 0.25), yielding a target of 30 patients per group. However, during the study period, the actual number of eligible patients was lower than this target; therefore, all available patients were included, resulting in a total of 51 participants across groups. These utility data have not been previously published and are presented here as original findings. In addition, utilities were applied as treatment-specific values, with quality-of-life differences reflected primarily during the PFS state, while the PD state was modeled uniformly across comparators (docetaxel followed by BSC). The costs and utility parameters are summarized in Table 1.

Transition probabilities

As no direct clinical trials were available comparing ceritinib, brigatinib, and alectinib with standard chemotherapy, treatment effectiveness was estimated from published literature[16,39–43]. Progression-free survival (PFS) and overall survival (OS) data were extracted and converted into transition probabilities, as shown in Table 2. The ASCEND-8 study demonstrated that the efficacy of ceritinib 450 mg/day with food was equivalent to ceritinib 750 mg/day without food[44]. Similarly, the efficacy of alectinib 600 mg/day was assumed to be comparable to alectinib 1,200 mg/day based on findings from the J-ALEX, ALEX, and ALESIA trials. These studies reported similar median PFS rates regardless of the administered dose[45].

Sensitivity analysis

To assess the model's robustness, both one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted. One-way sensitivity analysis results were illustrated using a Tornado diagram, while PSA incorporated beta distributions for transition probabilities and utilities and gamma distributions for costs. A cost-effectiveness acceptability curve (CEAC) was developed to demonstrate the probability of each cost-effective treatment at different WTP thresholds.

Parameters	Values	Range	Source
Direct medical costs; THB (USD)			
Drug cost (per cycle)			
Ceritinib (450 mg/day)	22,995 (626.71)	18,396 - 27,594 (500.57 - 750.86)	32
Ceritinib (750 mg/day)	38,325 (1,042.85)	30,660 - 45,990 (834.29–1,251.43)	32
Alectinib (600 mg/day)	76,623 (2,087.70)	61,298 - 91,947 (1,667.97 - 2,501.96)	32
Alectinib (1,200 mg/day)	153,245 (4,169.93)	122,596 - 183,894 (3,335.95–5,003.92)	32
Brigatinib (180 mg/day)	83,632 (2,275.70)	66,906 - 100,359 (1,820.57–2,730.86)	32
Carboplatin plus paclitaxel	2,880 (78.37)	2,304 - 3,456 (62.69 - 94.04)	32
Pemetrexed plus cisplatin	42,124 (1,146.23)	33,699 - 50,548 (916.98–1,375.46)	32
Pemetrexed plus carboplatin	42,796 (1,164.52)	34,237 - 51,356 (931.62–1,397.44)	32
Gemcitabine plus cisplatin	3,498 (95.18)	2,799 - 4,198 (76.16 - 114.23)	32
Gemcitabine plus carboplatin	4,171 (113.50)	3,337 - 5,006 (90.80 - 136.22)	32
Docetaxel	2,273 (61.85)	1,818 - 2,727 (49.47 - 74.20)	32
BSC	3,763 (102.39)	3,011 - 4,516 (81.93 - 122.88)	18
Hospital medical expenses			
Doctor fees (per visit)	283 (7.70)	226–339 (6.15 - 9.22)	34
Nursing services (per day)	67 (1.82)	54–80 (1.47–2.18)	34
Pharmacy dispensing fees (per prescription)	68 (1.85)	54–82 (1.47–2.23)	34
Chemotherapy preparation (per prescription)	262 (7.13)	210–315 (5.71 - 8.57)	34
Laboratory test (per cycle)	2,064 (56.16)	1,651- 2,477 (44.93 - 67.40)	18
Treatment of adverse events (per event)			
Anemia	6,029 (164.05)	-	33
Anorexia	322 (8.76)	-	33
Diarrhea	170 (4.62)	-	33
Dyspnea	33,615 (914.69)	-	33
Febrile neutropenia	50,000 (1,360.54)	-	33
Infection	1,050 (28.57)	-	33
Nausea	131 (3.56)	-	33
Vomiting	131 (3.56)	-	33
Pulmonary event	33,615 (914.69)	-	33
Rash	152 (4.14)	-	33
Direct non-medical costs (per visit); THB (USD)			
Transportation	142 (3.86)	114–171 (3.10–4.65)	34
Food	52 (1.39)	42–63 (1.14 - 1.71)	34
Utilities			
Ceritinib	0.800	0.58 - 1	Interview
Alectinib	0.808	0.701 - 1	Interview
Brigatinib	0.808	0.55 - 0.99	36,37
Carboplatin plus paclitaxel	0.417	−0.072 - 0.78	Interview
Pemetrexed plus cisplatin/carboplatin	0.574	0.264 - 0.723	Interview
Gemcitabine plus cisplatin/carboplatin	0.694	0.594 - 1	Interview
Docetaxel	0.513	0.246 - 0.78	Interview
BSC	0.191	−0.26 - 0.5	Interview

Table 1. Cost and utility parameters. Abbreviations: BSC, best supportive care; THB, Thai baht; USD, United States dollar.

Transition probability	Probabilities of disease progression			Probabilities of death		
	Mean	SE	Source	Mean	SE	Source
Brigatinib 1 st – 5th month	0.0109	0.00057	[39]	0.0065	0.00033	[39]
Brigatinib 6th - 10th month	0.0067	0.00037	[39]	0.0065	0.00033	[39]
Brigatinib 11th - 15th month	0.0057	0.00032	[39]	0.0130	0.00066	[39]
Brigatinib 16th - 20th month	0.0034	0.00017	[39]	0.0065	0.00033	[39]
Brigatinib 21 st - 30th month onward	0.0159	0.00083	[39]	0.0445	0.00227	[39]
Ceritinib 1 st – 5th month	0.0296	0.00151	[38]	0.0075	0.00038	[38]
Ceritinib 6th - 10th month	0.0193	0.00098	[38]	0.0075	0.00038	[38]
Ceritinib 11th - 15th month	0.0164	0.00084	[38]	0.0149	0.00076	[38]
Ceritinib 16th - 20th month	0.0090	0.00046	[38]	0.0075	0.00038	[38]
Ceritinib 21 st - 30th month onward	0.0426	0.00217	[38]	0.0511	0.00261	[38]
Alectinib 1 st – 5th month	0.0098	0.00050	[39]	0.0033	0.00017	[39]
Alectinib 6th - 10th month	0.0064	0.00033	[39]	0.0033	0.00017	[39]
Alectinib 11th - 15th month	0.0054	0.00028	[39]	0.0066	0.00034	[39]
Alectinib 16th - 20th month	0.0030	0.00015	[39]	0.0033	0.00017	[39]
Alectinib 21 st - 30th month onward	0.0140	0.00071	[39]	0.0225	0.00115	[39]
Carboplatin plus paclitaxel	0.1139	0.00581	[40]	0.0392	0.00168	[40]
Pemetrexed plus cisplatin/carboplatin	0.0316	0.00161	[16]	0.0130	0.00156	[16]
Gemcitabine plus cisplatin/carboplatin	0.0683	0.00348	[41]	0.0350	0.00179	[41]
Docetaxel	0.0571	0.00135	[42]	0.0464	0.00214	[42]
BSC	-	-	-	0.0494	0.00252	[43]

Table 2. Transition probability parameters Abbreviations: BSC, best supportive care; THB, Thai baht; USD, United States dollar; SE, standard error of the mean.

Budget impact analysis

A BIA was conducted over a five-year period from the payer perspective of the Universal Coverage Scheme (UCS), Thailand's major public health insurance payer. The number of patients with advanced ALK-positive NSCLC was estimated based on 23,713 new lung cancer cases reported by Globocan in 2020[1]. Approximately 90% (21,342 patients) were NSCLC cases[46]. According to Thailand's hospital cancer registry, approximately 50% of newly diagnosed lung cancer patients (10,671 patients) had advanced-stage disease, with an estimated 7% (747 patients) being ALK-positive, forming the BIA target population[46].

The BIA included only direct medical costs based on the payer perspective, including drug acquisition, BSC, hospital medical expenses, treatment of adverse events, and ALK gene screening. Comparators were standard chemotherapy regimens recommended by Thai clinical practice guidelines: carboplatin plus paclitaxel, gemcitabine plus cisplatin, and gemcitabine plus carboplatin.

The budget impact was calculated assuming all eligible patients would have full access to ALK inhibitors and complete the prescribed treatment regimen. Since epidermal growth factor receptor (EGFR)-positive and ALK-positive mutations are mutually exclusive[47], patients with advanced NSCLC undergoing initial EGFR mutation testing for treatment eligibility with erlotinib (a drug listed in Thailand's NLEM) are expected to have EGFR mutations in approximately 50% of cases, based on expert assessments. The remaining 50% of advanced NSCLC patients (5,336 cases) would then be eligible for ALK gene screening. As per Thai clinical guidelines, ALK gene screening is initially performed using immunohistochemistry (IHC), with confirmatory testing via fluorescence in situ hybridization (FISH). The cost of IHC testing for ALK rearrangements is 2,000 THB (54.42 USD) per test[48].

Code availability

Analyses were performed using Microsoft Excel Version 16.100.2 and TreeAge Pro Version 2024, which are commercially available software. No custom code was used in this study.

Results

Table 3 presents the analysis comparing ceritinib, brigatinib, and alectinib with standard chemotherapy. Among the evaluated regimens, carboplatin plus paclitaxel had the lowest total lifetime cost at 89,842 THB (2,445 USD) per patient. However, this regimen also yielded the poorest clinical outcomes, with 1.23 LYs and 0.46 QALYs gained. Alectinib resulted in 2.67 LYs and 2.00 QALYs gained, with a lifetime cost of 3,199,465 THB (87,060.14 USD) per patient for the 600 mg/day dose and 6,285,013 THB (171,021 USD) per patient for the 1,200 mg/day dose. None of the second-generation ALK inhibitors or pemetrexed-based chemotherapy regimens were cost-effective compared to chemotherapy at Thailand's WTP threshold. Ceritinib (450 mg/day) provided 1.96 LYs and 1.33 QALYs for 685,713 THB (18,659 USD), with an ICER of 1,101,441 THB/QALY (29,971 USD/QALY) compared to chemotherapy. Although ceritinib was the most cost-effective ALK inhibitors when compared to chemotherapy, it remained not cost-effective relative to chemotherapy under Thailand's WTP threshold.

Interventions	Lifetime costs: THB (USD)	Life years	QALYs	ICER THB (USD)/QALY
Carboplatin plus paclitaxel	89,842 (2,445)	1.23	0.46	
Gemcitabine plus cisplatin	96,078 (2,614)	1.30	0.67	29,999 (816)
Gemcitabine plus carboplatin	101,467 (2,761)	1.30	0.67	Dominated
Pemetrexed plus cisplatin	265,822 (7,233)	1.89	0.94	604,865 (16,459)
Pemetrexed plus carboplatin	269,300 (7,328)	1.89	0.94	Dominated
Ceritinib (450 mg/day)	685,713 (18,659)	1.96	1.33	1,101,441 (29,971)
Ceritinib (750 mg/day)	1,078,533 (29,348)	1.96	1.33	Dominated
Brigatinib (180 mg/day)	2,889,129 (78,616)	2.20	1.64	6,894,279 (187,599)
Alectinib (600 mg/day)	3,199,465 (87,060)	2.67	2.00	863,816 (23,505)
Alectinib (1,200 mg/day)	6,285,013 (171,021)	2.67	2.00	Dominated

Table 3. Lifetime costs, life years, QALYs and ICER of each intervention. Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; THB, Thai baht; USD, United States dollar. Dominated indicates that a treatment option is both more costly and less effective than the comparator, and therefore not considered cost-effective.

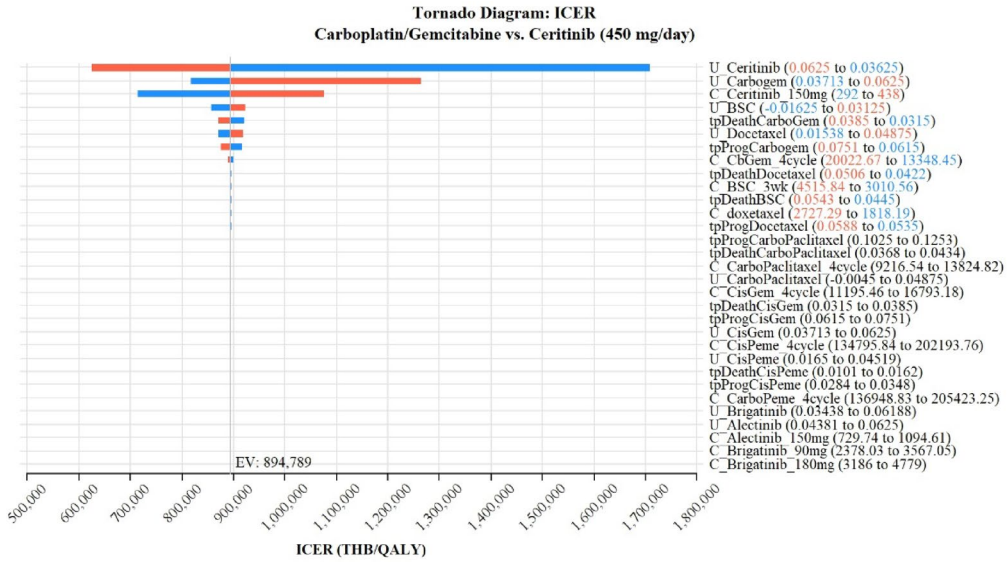

Fig. 2. Tornado diagram of Ceritinib.

Sensitivity analyses

The one-way sensitivity analysis identified three parameters that had the most significant impact on ICER fluctuations: the utility value of ALK inhibitors, the cost of ALK inhibitors, and the utility value of comparators. These results are illustrated in the tornado diagram (Figs. 2, 3 and 4). The PSA results confirmed that none of the ALK inhibitors were cost-effective compared to chemotherapy at the WTP threshold of 160,000 THB/QALY (4,353.74 USD/QALY). The cost-effectiveness acceptability curve (CEAC) (Fig. 5) demonstrated that at a WTP of 1,500,000 THB/QALY (40,816 USD/QALY), ceritinib (450 mg/day) was 75.5% likely to be cost-effective compared to chemotherapy. The threshold analysis indicated that if the price of ceritinib 450 mg were reduced by 60.27% and 82.34%, ceritinib would become a cost-effective compared to pemetrexed plus carboplatin and gemcitabine plus cisplatin, respectively.

Budget impact analysis

Table 4 presents the BIA results, which were reported as the total cost over a five-year horizon from the payer's perspective, in line with the national HTA guideline[29]. Among all ALK inhibitors, the five-year cost of treatment with ceritinib (450 mg/day) was the lowest at 2,345 million THB (63.81 million USD). However, this cost was still 2,035 million THB (55.38 million USD) higher than the cost of carboplatin plus paclitaxel. The highest budget requirement was associated with alectinib (1,200 mg/day), totaling 19,328 million THB (525.92 million USD) over five years. The estimated annual cost of ALK gene screening was 10.67 million THB (0.29 million USD), equating to 14,286 THB (388.73 USD) per newly diagnosed ALK-positive NSCLC case.

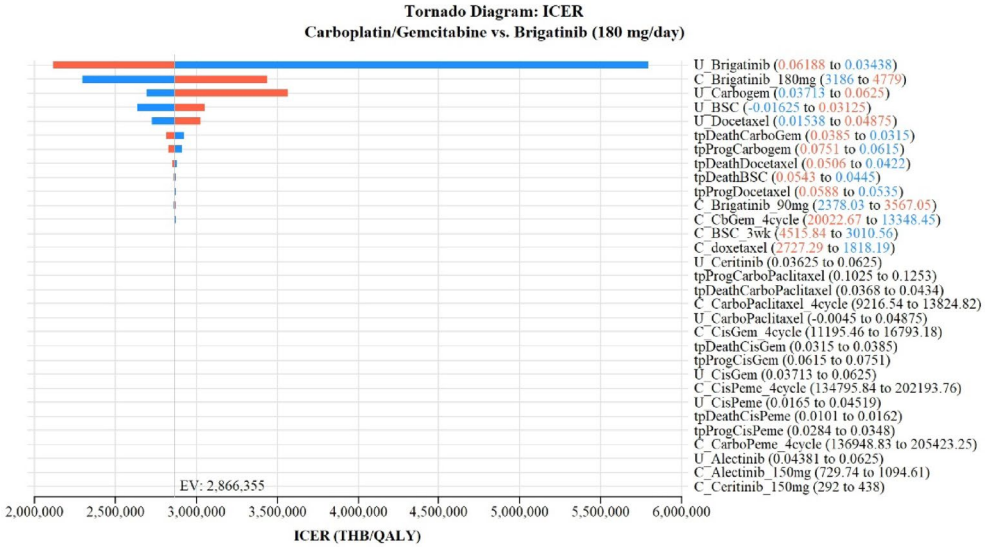

Fig. 3. Tornado diagram of Brigatinib.

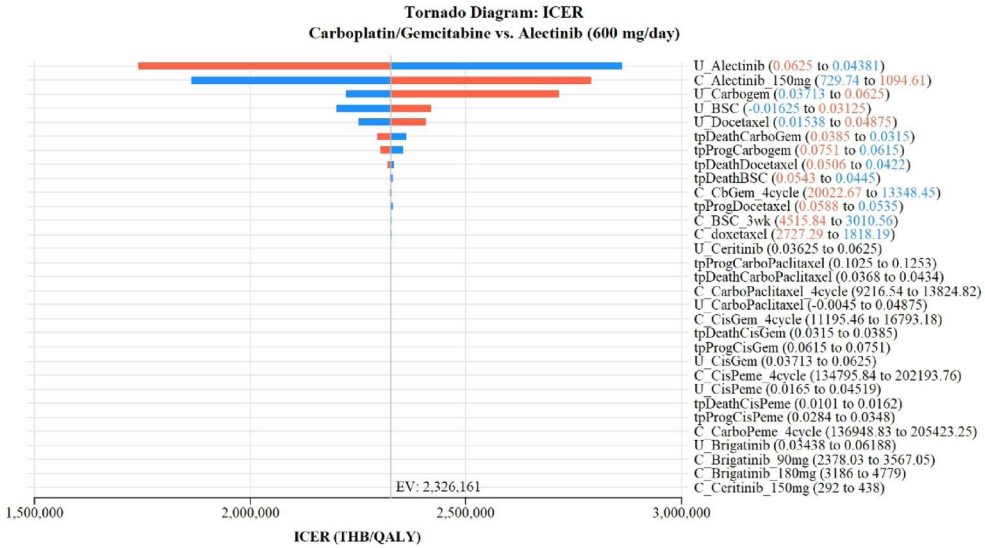

Fig. 4. Tornado diagram of Alectinib.

Discussion

This study assessed the cost-utility and BIA of ceritinib, brigatinib, and alectinib compared to standard chemotherapy for patients with advanced NSCLC in Thailand. The findings indicated that ceritinib, brigatinib, and alectinib were not cost-effective compared to chemotherapy at Thailand's WTP threshold of 160,000 THB/QALY (4,353.74 USD/QALY). Among the second-generation ALK inhibitors, ceritinib (450 mg/day) was the most cost-effective option across all comparisons. Over five years, the budget required for ceritinib (450 mg/day) was the lowest among the ALK inhibitors. However, this cost remained 2,035 million THB (55.38 million USD) higher than carboplatin plus paclitaxel. The annual budget required for ALK rearrangement gene screening was estimated at 10.67 million THB (0.29 million USD).

The results of this study were consistent with a study conducted by Peng et al. in 2019[49], which indicated that ceritinib was not a cost-effective option compared to platinum-based chemotherapy in China. However, several other studies have found that ceritinib was cost-effective in certain countries. According to reports by Hurry et al. in 2016[20] and Zhou et al. in 2018[21], ceritinib was considered to be a cost-effective option compared to chemotherapy in Canada and the United States, respectively. The study of Zhou et al. in 2018[21] and Loong et al. in 2020[22] found that ceritinib was also a cost-effective option compared to crizotinib in the United States and Hong Kong, respectively. Various factors contributed to the divergent study findings, including the research perspective, comparators, study design, the specific public health systems in different countries, and, more

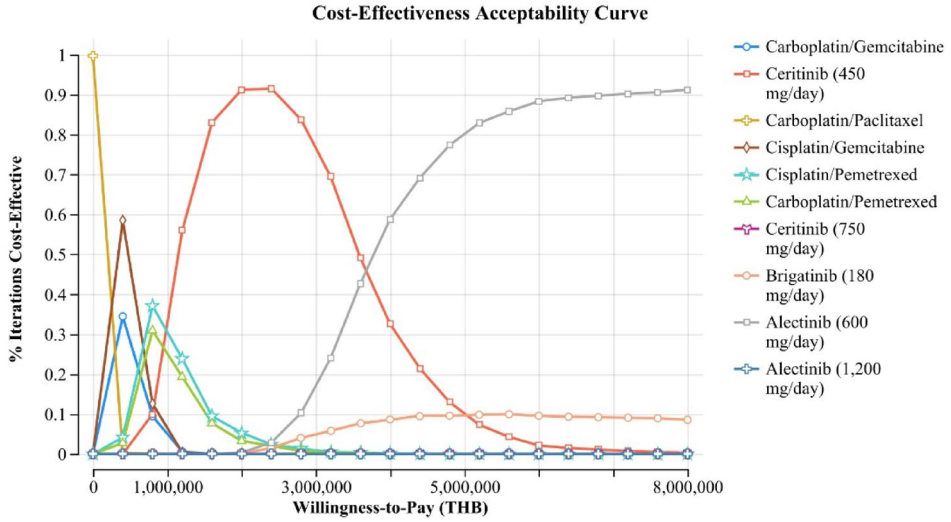

Fig. 5. The cost-effectiveness acceptability curve (CEAC).

Interventions	Million THB (million USD)					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Carboplatin plus paclitaxel	47 (1.28)	61 (1.65)	66 (1.79)	68 (1.85)	68 (1.86)	310 (8.43)
Gemcitabine plus cisplatin	50 (1.37)	64 (1.76)	70 (1.91)	72 (1.97)	73 (1.99)	331 (9.00)
Gemcitabine plus carboplatin	54 (1.48)	68 (1.86)	74 (2.02)	76 (2.08)	77 (2.10)	351 (9.55)
Pemetrexed plus cisplatin	163 (4.43)	182 (4.95)	192 (5.23)	198 (5.38)	200 (5.44)	935 (25.43)
Pemetrexed plus carboplatin	166 (4.50)	184 (5.02)	195 (5.30)	200 (5.45)	203 (5.51)	948 (25.79)
Ceritinib (450 mg/day)	323 (8.78)	460 (12.52)	512 (13.93)	524 (14.25)	526 (14.33)	2,345 (63.81)
Ceritinib (750 mg/day)	513 (13.96)	729 (19.84)	808 (22.00)	824 (22.43)	828 (22.53)	3,703 (100.76)
Brigatinib (180 mg/day)	1,173 (31.91)	1,800 (48.97)	2,104 (57.25)	2,198 (59.82)	2,227 (60.60)	9,502 (258.56)
Alectinib (600 mg/day)	1,111 (30.23)	1,764 (47.99)	2,163 (58.86)	2,352 (64.01)	2,440 (66.40)	9,830 (267.49)
Alectinib (1,200 mg/day)	2,186 (59.48)	3,470 (94.42)	4,254 (115.75)	4,623 (125.80)	4,794 (130.46)	19,328 (525.92)

Table 4. Budget impact analysis. Abbreviations: THB, Thai baht; USD, United States dollar.

importantly, the health system's ability to pay for health technology. The study's findings on alectinib were consistent with Sangroongruangsri et al. in 2022[50]. The study results indicated that using alectinib was not cost-effective compared to chemotherapy in the Thai context. Furthermore, this study was the first to assess the cost-effectiveness of brigatinib compared to standard chemotherapy, unlike previous literature reviews that did not find any studies directly comparing the two options.

It is noteworthy that prior research has analyzed the cost-effectiveness of ALK inhibitors across various countries. However, the majority of these studies assessed each ALK inhibitor independently and did not perform direct comparisons among second-generation ALK inhibitors. Therefore, our study addresses this gap in evidence by conducting head-to-head comparisons of multiple second-generation ALK inhibitors against chemotherapy, specifically adapted to the Thai healthcare setting. This emphasis on chemotherapy as the comparator strengthens the policy relevance of our findings, as chemotherapy remains the real-world first-line treatment in Thailand. Moreover, our findings suggest that ALK inhibitors are difficult to demonstrate as cost-effective because of their innovative nature and high acquisition costs. While these drugs significantly improve PFS and OS, the requirement for continuous treatment leads to escalating budgetary impact. Our review of the published literature on individual ALK inhibitors, along with our study's findings, shows that the evidence generally aligns with previous research in oncology[51,52]. This research also emphasizes the difficulties of proving cost-effectiveness for high-cost, innovative cancer treatments using traditional WTP thresholds.

Considering the existing challenges, potential policy solutions ought to be examined to enhance affordability and optimize value for money. A literature review on price negotiations for high-cost drugs in Thailand found that negotiated discounts for such medications typically range from 30% to 35%[53]. Notably, while the NCCN guidelines recommend full-dose administration of ALK inhibitors, real-world clinical practice among The Association of Southeast Asian Nations (ASEAN) populations often involves only half of the recommended dose. According to this study, using a half-dose strategy, combined with alternative funding mechanisms such as

price negotiations, could enhance the likelihood of ALK inhibitors being cost-effective within Thailand's WTP threshold.

This study has an unavoidable limitation regarding both utility data and effectiveness synthesis. Firstly, utility data for ceritinib, alectinib, chemotherapy, and BSC were collected from 51 patients at King Chulalongkorn Memorial Hospital using the Thai EQ-5D-5 L questionnaire. The small sample size within each group limits reliability and introduces uncertainty in utility estimates. Since no patients received brigatinib during the study period, its utility values were assumed comparable to alectinib and supplemented with published literature, with sensitivity analyses performed to test robustness. Despite the inherent variability in utility values, the overall findings remained consistent. Secondly, this study did not conduct a formal network meta-analysis. Treatment effectiveness was synthesized from individual published trials and indirect comparisons, which may introduce potential limitations related to heterogeneity of trial populations, differences in study protocols, and assumptions of transitivity. Additionally, the lack of direct head-to-head trials among ALK inhibitors contributes to uncertainty in the comparative effectiveness estimates used in the model. These factors should be considered when interpreting the results; however, the main findings of the study remained consistent across analyses. Although our study has its limitations, it remains highly credible, and the findings provide valuable insights for policymakers considering the listing of ALK inhibitors in the NLEM in Thailand.

Further studies should assess the cost-effectiveness and budget impact of lorlatinib, a third-generation ALK inhibitor, to provide a more comprehensive evaluation across treatment generations.

Conclusion

Second-generation ALK inhibitors, including ceritinib, brigatinib, and alectinib, were not cost-effective at Thailand's WTP threshold of 160,000 THB/QALY (4,353.74 USD/QALY). Although all ALK inhibitors yielded higher QALYs, the lifetime costs associated with their use cannot be offset by the additional outcomes gained. These findings provide valuable evidence to support policy decision-making regarding the reimbursement of ALK inhibitors in Thailand. Furthermore, the results highlight the need for alternative funding mechanisms, such as price negotiations and dose optimization strategies, to improve the affordability and accessibility of these targeted therapies.

Data availability

The utility datasets generated during and/or analysed during the current study are not publicly available due to privacy/ethical restrictions, but are available from the corresponding author on reasonable request.

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Author contributions

PL, NK, CV, and ST conceived the conception and design of the study. CV provided study material and patient information. PL, NP, SS, and NK analyzed and interpreted the data. PL and NK prepared the draft of the article. ST revised and approved the final version of the article.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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