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Effectiveness and cost-effectiveness of erlotinib versus gefitinib in first-line treatment of epidermal growth factor receptor–activating mutation-positive non–small-cell lung cancer patients in Hong Kong

Vivian WY Lee, Bjoern Schwander *, Victor HF Lee

**ABSTRACT**

**Objective:** To compare the effectiveness and cost-effectiveness of erlotinib versus gefitinib as first-line treatment of epidermal growth factor receptor–activating mutation-positive non–small-cell lung cancer patients.

**Design:** Indirect treatment comparison and a cost-effectiveness assessment.

**Setting:** Hong Kong.

**Patients:** Those having epidermal growth factor receptor–activating mutation-positive non–small-cell lung cancer.

**Interventions:** Erlotinib versus gefitinib use was compared on the basis of four relevant Asian phase-III randomised controlled trials: one for erlotinib (OPTIMAL) and three for gefitinib (IPASS; NEJGSG; WJTOG). The cost-effectiveness assessment model simulates the transition between the health states: progression-free survival, progression, and death over a lifetime horizon. The World Health Organization criterion (incremental cost-effectiveness ratio <3 times of gross domestic product/capita: <US$102 582; approximately <HK$798 078) was used to rate cost-effectiveness.

**Results:** The best fit of study characteristics and prognostic patient characteristics were found between the OPTIMAL and IPASS trials. Comparing progression-free survival hazard ratios of erlotinib versus gefitinib using only these randomised controlled trials in an indirect treatment comparison resulted in a statistically significant progression-free survival difference in favour of erlotinib (indirect treatment comparison hazard ratio=0.33; 95% confidence interval, 0.19–0.58; P=0.0001). The cost-effectiveness assessment model showed that the cost per progression-free life year gained and per quality-adjusted life year gained was at acceptable values of US$39 431 (approximately HK$306 773) and US$62 419 (approximately HK$485 619) for erlotinib versus gefitinib, respectively.

**Conclusion:** The indirect treatment comparison of OPTIMAL versus IPASS shows that erlotinib is significantly more efficacious than gefitinib. Furthermore, the cost-effectiveness assessment indicates that the incremental cost-effectiveness ratios are well within an acceptable range in relation to the survival benefits obtained. In conclusion, erlotinib is cost-effective compared to gefitinib for first-line epidermal growth factor receptor–activating mutation-positive non–small-cell lung cancer patients.

New knowledge added by this study

- The current project provided cost-effectiveness information for erlotinib and gefitinib based on four Asian phase-III clinical trials in non–small-cell lung cancer (NSCLC) patients using a threshold recommended by the World Health Organization.
- The cost-effectiveness analysis indicates that erlotinib is cost-effective compared to gefitinib in first-line epidermal growth factor receptor (EGFR)–activating mutation-positive (MuT+) NSCLC patients in Hong Kong.

Implications for clinical practice or policy

- Erlotinib is efficacious and cost-effective, and hence should be considered a good option for treatment of EGFR MuT+ NSCLC patients.
- Being cost-effective, erlotinib should be considered for reimbursement by health care payers in Hong Kong.
Introduction

Lung cancer is the leading cause of cancer deaths worldwide (1.38 million cancer deaths, 18.2% of the total) as well as of cancer morbidity (1.61 million new cases, 12.7% of all new cancers). Approximately 80% to 85% of lung cancer patients have non-small-cell lung cancer (NSCLC), and around 70% of these NSCLC patients present with advanced or metastatic disease (TNM stages IIIB/IV according to the American Joint Committee on Cancer) at the time of diagnosis. 

Evidently, NSCLC is a biological and genetic variant of lung cancer, which bears activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). In Asian NSCLC patients, the frequency of activating EGFR mutations (EGFR MuT+) is estimated to be approximately 30% to 40%. Notably, EGFR mutations (EGFR MuT+) is estimated to be approximately 30% to 40%. 

In order to base the research on the strongest available evidence, standard literature databases (PubMed, ASCO and ESMO congress databases) were screened for Asian randomised controlled phase-III trials that investigated the efficacy of erlotinib and gefitinib as first-line EGFR MuT+ NSCLC therapy. We included all Asian randomised controlled phase-III trials that investigated either gefitinib or erlotinib as first-line therapy of NSCLC, that have systematically assessed the EGFR mutation status of the included patients, and that have published sufficient information on the EGFR-mutation patient population characteristics and outcomes. By applying these criteria, four suitable Asian phase-III randomised controlled trials (RCT) were identified, one for erlotinib and three for gefitinib.

The OPTIMAL trial evaluated the efficacy and tolerability of erlotinib versus chemotherapy, and the Iressa Pan-Asia Study (IPASS), the North-East Japan Gefitinib Study Group trial (NEJGSG), and the West Japan Thoracic Oncology Group 3405 trial (WJTOG) evaluated the efficacy and safety of gefitinib versus chemotherapy. The following section provides the background information on these clinical trials, which is necessary as a basis for the planned comparative assessments.

Study characteristics, study measurements, and patient characteristics

As shown in Table 1, the main study characteristics,
study measurements, and patient characteristics of the Asian EGFR TKI phase-III RCT for first-line treatment of EGFR MuT+ NSCLC were largely comparable but not identical.12,14-16

The best fit is encountered with the OPTIMAL and IPASS trials, as the tumour assessment periodicity (6 weekly for both OPTIMAL and IPASS), median age (57 years for both trials), performance status proportion (performance status 0 or 1: OPTIMAL 92%, IPASS 90%), and the tumour stage distribution (stage IV: OPTIMAL 87%, IPASS 86%) were comparable. In contrast, on comparing OPTIMAL versus the NEJGSG and WJTOG trials, differences were evident with respect to all of the above-named factors (Table 1). Such differences are important, as at least age, performance status, and tumour stage were predictors of progression-free survival (PFS) in NSCLC.7,17-19

**Efficacy outcomes**

All these phase-III RCT in first-line EGFR MuT+ NSCLCs have shown significant increases in the primary endpoint, namely PFS for erlotinib (OPTIMAL trial12) and gefitinib (IPASS14, NEJGSG15, WJTOG16) in comparison to standard chemotherapy. The erlotinib OPTIMAL trial reached a median PFS of 13.7 months and a corresponding hazard ratio (HR) of 0.16 with 95% confidence intervals (CI) of 0.11-0.26 (P<0.001).13 The gefitinib IPASS, NEJGSG, and WJTOG trials reached a respective median PFS of 9.5, 10.8, and 8.4 months with corresponding HRs of 0.48 (95% CI, 0.36-0.64; P<0.001), 0.30 (95% CI,
treatment comparison (ITC), as this efficacy measurement accounts for censoring and incorporates time-to-event information. As an outcome of the comparative effectiveness assessment, the ITC HRs of erlotinib versus gefitinib are provided with 95% CIs. The applied ITC approach uses an effect size (PFS HR) that is expressed relative to the comparator (A vs C and B vs C; hence the comparator is used as a ‘bridge’) to perform a so-called ‘adjusted ITC’ of the investigational treatment arms (A vs B). The related formula for the ITC HR is $HR_{AB} = HR_{AC}/HR_{BC}$ and the formula for the ITC 95% CI is $HR_{AB} \pm 1.96 \times \text{SQRT}(\text{VAR}[HR_{AB}])$.

In order to test for statistical significance, P values were calculated by means of a two-sided Z test, using the methodology of Snedecor and Cochran 1989. The null hypothesis that the PFS of the compared therapy options is equal was to be rejected if $P<0.05$. All calculations were performed using Excel 2003. The ITC calculations could be re-performed using the ITC tool provided by the Canadian Agency for Drugs and Technologies in Health, thus ensuring maximum transparency.

Due to the good fit in prognostic patient characteristics, the key ITC was based on the OPTIMAL versus IPASS phase-III PFS HR outcomes. Furthermore, OPTIMAL was compared with the pooled Asian gefitinib evidence. This pooled evidence was obtained by applying a random effect pooling (PFS HR of gefitinib vs chemotherapy $= 0.37$; 95% CI, 0.27-0.51; $P<0.0001$) and a fixed effect pooling (PFS HR of gefitinib vs chemotherapy $= 0.38$; 95% CI, 0.31-0.46; $P<0.0001$) to the PFS HR outcomes of the IPASS, NEJGSG, and WJTOG trials.

**Cost-effectiveness assessment**

Phase-III RCT evidence was used as the basis for the CEA. Evidence from OPTIMAL was used for erlotinib and evidence from IPASS for gefitinib, as these studies were the most comparable with respect to prognostic characteristics of the patients (Table 1).

The CEA model uses a Markov approach that simulates the transition between the health states: PFS, progression and death, in monthly cycles and over a lifetime horizon. Patients with stage IIIb/IV EGFR MuT+ NSCLC enter the model in PFS. Transition from PFS to progression is simulated by the published phase-III Kaplan-Meier estimates (erlotinib: OPTIMAL; gefitinib: IPASS). For the transition from progression to death, the same transition probability was applied for both EGFR TKIs using the final overall survival results from IPASS. This procedure was necessary, as OPTIMAL survival data are currently immature and follow-up is ongoing.

To estimate the Hong Kong–specific drug costs, the licensed dosage (same as in the phase-III RCT) was applied; hence a daily dose of 150 mg for erlotinib and a daily dose of 250 mg for gefitinib were simulated. The drug costs per daily dose of US$74.94 for erlotinib and US$59.98 for gefitinib were based on gross ex-factory prices from October 2011. In order to transfer the local currency (HK$) to US$, the average exchange rates (October 2010 to October 2011) from the Reserve Bank of Australia were simulated. The drug costs per daily dose of $0.22-0.41; $P<0.001$, and 0.33 (95% CI, 0.20-0.54; $P<0.0001$).

**Tolerability outcomes**

According to all four phase-III RCT, the EGFR TKIs showed a better tolerability profile than the chemotherapy comparators, and hence they appeared to confer less toxicity while achieving greater efficacy. The most common serious adverse event (SAE) reported for erlotinib is elevation of alanine aminotransferase level (3.6%), which nevertheless compares favourably with gefitinib (27.6%). Other SAEs with the highest frequency for erlotinib also compare favourably with gefitinib, namely rash (2.4% vs 5.3%) and diarrhoea (1.2% vs 3.8%). Infection is the only SAE that has been reported for erlotinib (1.2%) but not in gefitinib trials. All other SAEs reported for gefitinib (aspartate aminotransferase elevation, neutropenia, fatigue, anaemia, anorexia, leukopenia, nausea, paronychia, and sensory disturbance) have not been reported for erlotinib. Irrespective of the small deviations observed when comparing the frequency of single adverse effects between erlotinib and gefitinib, the toxicity of these two TKIs can be regarded as comparable.

**Methods**

**Comparative effectiveness assessment**

As both EGFR TKIs have shown favourable outcomes compared to chemotherapy, both are currently competing to be the primary choice in treatment-naive EGFR MuT+ NSCLC patients. Thus, in the absence of a direct head-to-head comparison, there is a need for an indirect comparative effectiveness assessment.

This assessment used the accepted and most widely applied indirect comparison methods introduced by Bucher et al in 1997. The Canadian Agency for Drugs and Technologies in Health and others have identified this method as the most suitable approach for performing indirect comparisons of RCT outcomes.

According to the Bucher method, the chemotherapy comparator arm (C) of each trial has been used as a ‘bridge’ to connect and compare the efficacy of the investigational treatment arms, namely erlotinib (A) and gefitinib (B). The PFS HRs were selected as the basis for this indirect treatment comparison (ITC), as this efficacy measurement accounts for censoring and incorporates time-to-event information. As an outcome of the comparative effectiveness assessment, the ITC HRs of erlotinib versus gefitinib are provided with 95% CIs. The applied ITC approach uses an effect size (PFS HR) that is expressed relative to the comparator (A vs C and B vs C; hence the comparator is used as a ‘bridge’) to perform a so-called ‘adjusted ITC’ of the investigational treatment arms (A vs B). The related formula for the ITC HR is $HR_{AB} = HR_{AC}/HR_{BC}$ and the formula for the ITC 95% CI is $HR_{AB} \pm 1.96 \times \text{SQRT}(\text{VAR}[HR_{AB}])$.

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were used (1 US$ = 7.78 HK$). These drug costs have been simulated until disease progression or death (therapy until progression).

In order to simulate quality-adjusted life years (QALYs), published health utility values according to Nafees et al.\(^{28}\) were applied to the health states of PFS (0.653) and progression (0.473). A health utility of zero (0) was applied to the health state of death. The CEA outcomes were expressed as cost per life year gained, cost per progression-free life year (PF-LY) gained, and as cost per QALY gained for erlotinib and gefitinib. The simulation results were based on a Monte-Carlo simulation using 1000 iterations; all simulations were performed in Excel 2003. Costs and effects have been discounted by 3% per annum according to regional pharmacoeconomic recommendations.\(^{29}\) Sensitivity analyses of the treatment effect on the cost-effectiveness results were performed by applying the extreme bounds (lower and upper 95% CIs) of the PFS Kaplan-Meier estimates for erlotinib and gefitinib.

The World Health Organization (WHO) criterion (incremental cost-effectiveness ratio [ICER] <3 times of the Hong Kong GDP/capita,\(^{30}\) which gave a figure of <US$102,582 or approximately <HK$798,078) was used for this purpose.\(^{31}\)

**Results**

**Comparative effectiveness assessment**

Comparing the PFS HRs of erlotinib versus gefitinib in first-line EGFR MuT+ NSCLC based on OPTIMAL and IPASS resulted in a statistically significant PFS difference in favour of erlotinib (ITC HR=0.33; 95% CI, 0.19-0.58; \(P=0.0001\)). As shown in Figure 1, comparing erlotinib versus the pooled gefitinib phase-III evidence confirmed these findings.

**Cost-effectiveness assessment**

According to the CEA model outcomes, erlotinib was more effective in terms of life years gained, PF-LY gained, and QALYs gained when compared with gefitinib in first-line EGFR MuT+ NSCLC therapy (Table 2).

The therapy costs of erlotinib were higher than those of gefitinib, as shown in Table 2. Besides higher daily therapy costs, the superior efficacy of erlotinib was the reason for this cost difference. The longer time in PFS compared with gefitinib increased its total therapy duration (therapy until the disease progressed or death), which translated into higher total costs.

To determine whether the additional total therapy costs of erlotinib therapy were reasonable in relation to the efficacy benefit obtained, an incremental cost-effectiveness analysis was performed. The cost per life year gained by erlotinib was US$41,494 (incremental costs US$14,061/incremental life years 0.34), the cost per PF-LY gained by erlotinib was US$39,431 (incremental costs US$14,061/incremental PF-LY 0.36), and the cost per QALY gained by erlotinib was US$62,419
(incremental costs US$14 061/incremental QALY 0.23) [Fig 2].

These ICERs were well within a range usually regarded as cost-effective using WHO cost-effectiveness criteria. According to these, a therapy is ‘highly cost-effective’ if the ICERs are less than the gross domestic product (GDP) per capita (<US$34 194), ‘cost-effective’ if the ICERs are between 1 (US$34 194) and 3 times (US$102 582) the GDP per capita, and ‘not cost-effective’ if more than 3 times the GDP per capita (>US$102 582).

As shown in Table 3, sensitivity analyses on the treatment effect confirmed the robustness of the cost-effectiveness outcomes as almost all ICERs remained below the WHO cost-effectiveness threshold (<US$102 582).

**Discussion**

To offer guidance for physicians and health care payers, comparative effectiveness and CEAs were

<table>
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<th>TABLE 3. Overview of discounted cost-effectiveness assessment model sensitivity analyses results simulated on the basis of the OPTIMAL and IPASS phase-III randomised controlled trials</th>
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<tr>
<td><strong>Erlotinib</strong></td>
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<td><strong>Base case</strong></td>
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<td>Total costs (US$)</td>
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<td>Life years</td>
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<td>Progression-free life years</td>
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<td><strong>Best PFS (upper 95% CI PFS)</strong></td>
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<td><strong>Worst PFS (lower 95% CI PFS)</strong></td>
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<td>Total costs (US$)</td>
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<td>Life years</td>
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<td><strong>Best PFS (ERL) vs base case (GEF)</strong></td>
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<td><strong>Best PFS (GEF) vs base case (ERL)</strong></td>
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<td>Quality-adjusted life years</td>
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Abbreviations: 95% CI = 95% confidence interval; ERL = erlotinib; GEF = gefitinib; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival.
performed to compare erlotinib versus gefitinib in the treatment of treatment-naïve patients with EGFR MuT+ NSCLC in the health care setting of Hong Kong. Both the comparative assessments used state-of-the-art methods; however, specific limitations had to be taken into account.

The main limitation related to these comparative effectiveness assessments was that our findings were based on indirect evidence. Such ITCs have to be regarded as complementary to clinical trials, because they cannot substitute direct evidence. However, in the absence of any head-to-head comparison, the ITC approach can be regarded as the most valuable way of estimating comparative treatment effects in a statistically accurate manner.

Another limitation was the difference in prognostic patient characteristics between the phase-III trials used. Whereas OPTIMAL and IPASS showed a relatively good fit, the OPTIMAL versus NEJGSG or WJTOG comparisons showed a mismatch of prognostic factors. For this reason, the comparative effectiveness assessment used only the OPTIMAL and the IPASS trials as a basis for the key comparison. Focusing on this key comparison was a necessary precondition for the validity of the ITC, as it ensured that the results were primarily influenced by the treatment effect and not the ‘base risk profiles’. To avoid this confounding factor, the NEJGSG and the WJTOG trials were only considered in a pooled gefitinib PFS HR analysis, which confirmed the findings of the key comparison (OPTIMAL vs IPASS).

Another Asian study, namely the First-SIGNAL study,32 was excluded from our assessment because relevant details on the EGFR MuT+ subpopulation were not published. Besides, the EGFR MuT+ status in this study was assessed only in a limited number of patients and the trial failed to meet its primary endpoint. However, an inclusion of First-Signal study would have worsened the pooled gefitinib results presented in our assessment, as the PFS HR obtained for the EGFR MuT+ population in First-SIGNAL study was the highest obtained within each gefitinib study (PFS HR = 0.54; 95% CI, 0.27-1.10) and did not reach statistical significance compared to chemotherapy.

For erlotinib, there was another phase-III RCT available named EURTAC that was performed in a European patient population, and resulted in a PFS HR of 0.37 (95% CI, 0.25-0.54),33 which was not included in our assessment. Compared with patients in the Asian phase-III gefitinib trials,14-16 patients in the EURTAC trial33 had the highest median age, the highest proportion with a worse performance status, and the highest proportion with stage IV disease, apart from using a Caucasian patient population which in itself was an important prognostic factor.34-36 Thus, according to these prognostic patient characteristics, the only phase-III trial performed in Caucasian patients (EURTAC) was not comparable to any other phase-III trial and hence warranted assessment separately from the Asian evidence. Notably, this was our rationale for basing our assessment for the Hong Kong health care setting on the available Asian evidence only.

The median PFS values of the chemotherapy comparator arms of the selected Asian phase-III trials were 4.6 months in OPTIMAL,12,13 5.4 months in NEJGSG,15 and 6.3 months in the IPASS14 and WJTOG.16 These differences in the median PFS times of chemotherapy have raised doubts about the PFS HRs of the OPTIMAL trial, since it seemed that erlotinib treatment was compared to a comparator arm with the worst performance. This is a frequently applied misinterpretation of the data, as the median PFS values reflect only one point in time in the PFS Kaplan-Meier curve. In order to determine whether one chemotherapy arm shows a better performance than the other (eg comparison between the OPTIMAL chemotherapy arm and the IPASS chemotherapy arm), a comparison of both chemotherapy PFS curves over time on the basis of patient level data from both clinical studies is required. Our comparison approach was based on the HRs (the standard measure for determining the efficacy of oncology drugs), which reflects the area between the PFS Kaplan-Meier curves of the EGFR TKIs versus the chemotherapy comparators, taking into account the whole study period, hence it is not influenced by the different median PFS values.

A possible reason for the PFS difference observed between the two EGFR TKIs might be related to the differences in the chemical structure of erlotinib and gefitinib. These structural differences influence the metabolism of the two drugs by the human liver enzymes. Erlotinib is less susceptible to the metabolizing enzymes than gefitinib and therefore, at an approved dose of 150 mg once daily, it achieves approximately a 3.5-fold higher steady-state plasma concentration than gefitinib administered at the recommended dose of 250 mg once daily.27 This higher circulating level of erlotinib might provide a clinical advantage over gefitinib38 and explain the better efficacy of erlotinib39 compared with gefitinib in the treatment-naïve Asian EGFR MuT+ NSCLC patients.

One limitation of the CEA performed was that total therapy costs were only estimated on the basis of drug costs. In order to perform an adequate total cost assessment, further cost components such as prescription costs, adverse effect costs, and EGFR mutation testing costs usually have to be taken into account. However, as the cost-effectiveness analysis was based on an incremental assessment of erlotinib versus gefitinib, the correctness of results depended on assessing all relevant differences in costs. These differences were considered adequately reflected
by differences in drug costs and differences in the therapy duration (difference in PFS) simulated. The rationale for this was that both therapies have comparable prescription and EGFR testing costs, which make no difference when calculating the incremental costs between the two therapies. Only the costs of adverse effects might influence the incremental costs. However, these costs are hard to assess. Although erlotinib shows less SAEs than gefitinib, the difference in the related costs in favour of erlotinib was estimated to be minor.

Another limitation of the cost-effectiveness analysis was the assumption that both TKI therapies present a similar survival probability after disease progression. The survival probability after disease progression was simulated on the basis of the IPASS overall survival outcomes. This assumption was necessary, as the overall survival results from OPTIMAL are still immature. As a result of this assumption, the PFS benefit of erlotinib was transferred to the overall survival outcome. How strongly this assumption impacts the results is currently difficult to determine. Future CEAs using the final OPTIMAL overall survival data (currently immature) are necessary to eliminate this uncertainty.

Furthermore, the cost-effectiveness results are not transferable to other health care settings, as they are dependent on country-specific drug prices. Hence, the results presented have to be regarded as specific to the health care setting of Hong Kong and any possible similar findings in other countries and health care settings need to be confirmed in separate analyses.

To the authors’ knowledge, this is the first ITC and CEA performed for treatment-naïve EGFR MutT+ NSCLC in Asian patients. Hence, currently there are no other publications confirming or conflicting with these findings.

Conclusion

The CEA for Hong Kong showed that the cost per life year gained, the cost per PF-LY gained, and the cost per QALY gained by erlotinib were well within an acceptable range in relation to the survival benefit obtained. In conclusion, erlotinib was cost-effective compared to gefitinib as first-line EGFR MutT+ NSCLC in Hong Kong.

Declaration

This work was funded by Roche Hong Kong Limited (Roche). Roche was involved in gathering the country-specific input data, and in reviewing and commenting the manuscript. All the authors made the decision to submit the manuscript for publication and guarantee the accuracy and completeness of the data. Prof Vivian WY Lee has received educational grant, research contracts, and donations from pharmaceutical companies including AstraZeneca, Boehringer Ingelheim, Eisai, Janssen, Pfizer, Novartis, and Roche.

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