Health economic analysis of epidermal growth factor receptor mutation-guided first-line therapies for advanced non-small-cell lung cancer: abridged secondary publication

JHS You *, WCS Cho, YC Li, CK Kwan, JSK Au

KEY MESSAGES

1. *EGFR* mutation-guided use of tyrosine kinase inhibitor (TKI) therapy (afatinib, erlotinib and gefitinib) appears to gain higher quality-adjusted life-years than empirical chemotherapy (without *EGFR* mutation testing).
2. The cost-effectiveness of *EGFR* mutation-guided TKI is highly subject to the cost of TKI therapy and the willingness-to-pay threshold.

Hong Kong Med J 2023;29(Suppl 2):S8-11
HMRF project number: 15160531

[1] JHS You, [2] WCS Cho, [3] YC Li, [4] CK Kwan, [5] JSK Au

[1] *School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China*
[3] *Hong Kong United Oncology Centre, Hong Kong SAR, China*
[4] *Department of Oncology, United Christian Hospital, Hong Kong SAR, China*
[5] *Oncology Center, Hong Kong Adventist Hospital, Hong Kong SAR, China*

* Principal applicant and corresponding author: joyceyou@cuhk.edu.hk

Introduction

In Hong Kong, lung cancer is the second most common cancer, with the highest mortality (crude rate, 52.6 per 100 000 persons) among the top 10 cancers.[1] Approximately 85% to 90% of lung cancers are classified as non-small-cell lung cancer (NSCLC), and approximately 80% of NSCLC are diagnosed in advanced stage of IIIB/IV. Standard platinum-based chemotherapy for advanced NSCLC can modestly lengthen survival by a few months.

Epidermal growth factor receptor (*EGFR*) gene mutations are actionable targets in NSCLC.[2] These mutations are correlated with treatment response to tyrosine kinase inhibitor (TKI) therapy. This study aims to compare the *EGFR* mutation-guided use of afatinib, erlotinib, and gefitinib versus empirical chemotherapy as first-line treatment of advanced NSCLC in Hong Kong.

Methods

A Markov model was designed to simulate outcomes of a hypothetical cohort of advanced (stage IIIB/IV) NSCLC adult patients with untested *EGFR*-sensitising mutation status (Fig 1). Four treatment strategies were evaluated: empirical first-line chemotherapy and *EGFR* mutation-guided use of afatinib, erlotinib, and gefitinib. The model time horizon was 10 years (with monthly cycle), and outcome measures were direct medical cost, progression-free survival, life-years, and quality-adjusted life-years (QALYs)

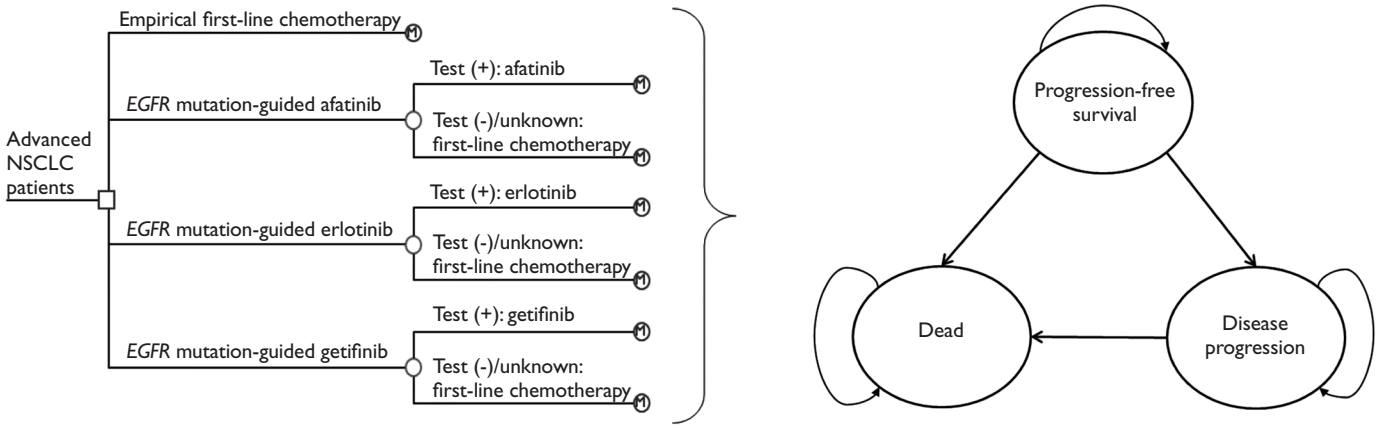

FIG 1. Simplified Markov model of empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer (NSCLC)

gained by each treatment strategy.

The literature on MEDLINE over the period 2000 to 2020 was searched using keywords: advanced non-small-cell lung cancer, NSCLC, *EGFR* mutation, overall survival, progression-free survival, first-line treatment, first-line chemotherapy, gefitinib, erlotinib, and afatinib. Selection criteria of clinical trials were: (1) in English language, (2) adult patients with stage IIIB/IV NSCLC, and (3) provision of progression-free survival, overall survival or adverse event rates.

The QALYs expected by each subject was estimated from cumulative subject-time spent in a heath state and the health state-specific utility value. The health states included progression-free survival, disease progression, and death, further adjusted with disutility of treatment-related serious adverse events (SAEs). The QALY gained was discounted by an annual rate of 3%.

Health economic analysis was conducted on direct medical costs from the perspective of Hong Kong public healthcare provider. Healthcare resource utilisation during progression-free survival and disease progression was estimated retrospectively. Medical record review was conducted for 400 patients aged ≥18 years with diagnosis of advanced (stage IIIB/IV) NSCLC who were treated with first-line chemotherapy (n=200, 58% male, mean age 67±12 years) or TKI (n=200, 56% male, mean age 66±12 years) in 2013 to 2017 at Queen Elizabeth Hospital and United Christian Hospital. Healthcare resource utilisation was collected to estimate monthly direct medical costs for progression-free survival state and disease progression state, and management cost per episode of treatment-related SAEs. The costs accumulated were discounted with an annual rate of 3%.

Base-case analysis compared the expected direct medical cost and QALYs of each *EGFR* mutation-guided TKI therapy with those of the empirical chemotherapy. A treatment strategy was dominated when it gained lower QALYs at higher cost than another option, and the dominated option was eliminated from further cost-effectiveness analysis. If a treatment strategy gained additional QALYs at higher cost than another alternative, incremental cost-effectiveness ratio (ICER) of the more effective strategy was calculated: ICER=Δcost/ΔQALYs.

The World Health Organization recommends that ICER <1× gross domestic product (GDP) per capita is highly cost-effective and <3× GDP per capita is cost-effective. The GDP per capita of Hong Kong was USD47 812 in 2019 and thus USD143 436 (3× GDP per capita) was used as the willingness-to-pay (WTP) threshold in the base-case analysis. A treatment alternative was preferred if it was effective in saving QALYs at lower cost or if it was effective in saving QALYs at higher cost and the ICER was below WTP threshold.

Sensitivity analysis was performed by TreeAge Pro 2020 to examine the robustness of the model results. One-way and probabilistic sensitivity analyses and scenario analysis were conducted.

Results

EGFR mutation-guided use of all three TKIs (afatinib, erlotinib, gefitinib) gained higher QALYs than empirical chemotherapy (Table). Compared with empirical chemotherapy, *EGFR* mutation-

TABLE. Base-case analysis for empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer

Base-case analysis	Empirical chemotherapy	*EGFR* mutation-guided erlotinib therapy	*EGFR* mutation-guided gefitinib therapy	*EGFR* mutation-guided afatinib therapy
Direct costs, USD	21 355	18 487	25 760	35 570
Progression-free survival, mo	8.67	15.78	14.30	16.79
Overall survival, mo	33.30	34.18	30.98	34.50
Quality-adjusted life-years (QALYs)	1.6358	1.8072	1.6464	1.8388
Versus empirical chemotherapy				
Incremental cost, USD	-	-2868	4405	14 215
Incremental QALYs	-	0.1714	0.0106	0.2030
incremental cost-effectiveness ratio, USD per QALY	-	Dominating empirical therapy	415 566	70 025
Versus the next less costly strategy				
Incremental cost, USD	2868	-	7273	17 083
Incremental QALYs	-0.1714	-	-0.1608	0.0316
Incremental cost-effectiveness ratio, USD per QALY	Dominated by *EGFR* mutation-guided erlotinib therapy	-	Dominated by *EGFR* mutation-guided erlotinib therapy	540 601

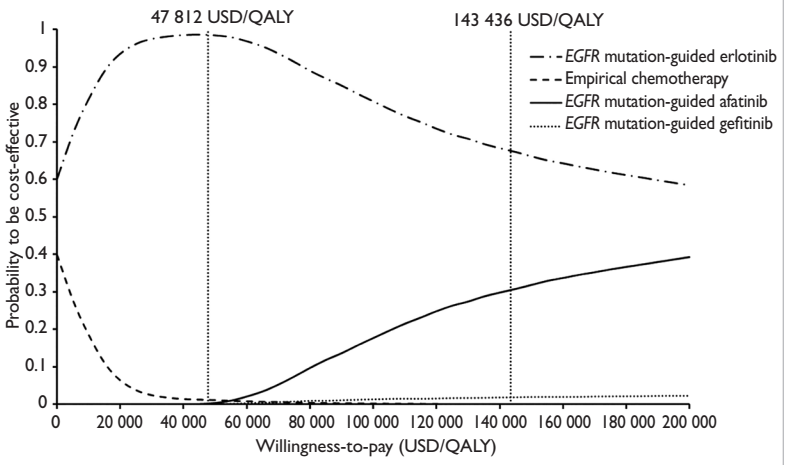

FIG 2. Acceptability curves of empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer (NSCLC) to be cost-effective against willingness-to-pay in USD/quality-adjusted life-years (QALY)

guided erlotinib gained higher QALYs with cost-saving, and the ICER of afatinib was lower than WTP threshold (143 436 USD/QALY). Both strategies of *EGFR* mutation-guided erlotinib and afatinib were cost-effective. *EGFR*-guided gefitinib gained higher QALY than empirical chemotherapy at an ICER (415 566 USD/QALY) exceeding WTP.

One-way sensitivity analysis found the base-case results robust to the variation of all model inputs. The *EGFR* mutation-guided afatinib therapy gained the highest QALYs with ICER exceeding the WTP threshold. The monthly cost of afatinib therapy was examined in extended one-way sensitivity analysis from the base-case value to a lower limit for identification of threshold value. The ICER of *EGFR* mutation-guided afatinib therapy became lower than the WTP threshold (and cost-effective) when the monthly cost of afatinib therapy was reduced by 56%. There was no threshold cost for EGFR mutation-guided gefitinib therapy because it was less effective.

In probabilistic sensitivity analysis with 10 000 Monte Carlo simulations, the acceptability of four treatment arms was examined simultaneously. Probabilities of each treatment strategy to be accepted as cost-effective are showed in the acceptability curves over a wide range of WTP (0-200 000 USD/QALY) [Fig 2].

EGFR mutation-guided therapies of afatinib, erlotinib, and gefitinib as well as empirical chemotherapy were accepted to be preferred strategy in 0.13%, 98.63%, 0.01%, and 1.23% of time at WTP 47 812 USD/QALY (1× GDP per capita), and in 30.54%, 67.54%, 1.79%, and 0.13% of time at WTP 143 436 000 USD/QALY (3× GDP per capita), respectively.

Two scenarios were examined. In scenario 1, public payer's perspective was applied on self-financed drugs (not subsidised by public payer). *EGFR* mutation-guided erlotinib therapy was preferred, with highest probability to be cost-effective when the WTP threshold was <81 470 USD/QALY. In scenario 2, a fifth study arm was added to examine *EGFR* mutation-guided TKI as the downstream treatment for patients who progressed on first-line empirical chemotherapy. *EGFR* mutation-guided erlotinib therapy was preferred, with highest probability to be cost-effective throughout the variation of WTP.

Discussion

A cost-effectiveness analysis of afatinib, gefitinib, or erlotinib therapy and first-line chemotherapy for *EGFR* mutation-positive NSCLC patients was reported in China.[3] The QALY gain was highest with afatinib, followed by erlotinib, gefitinib, and chemotherapy. Our findings on the highest QALY gain by the afatinib therapy are consistent with those reported in China. In the present study, erlotinib therapy was accepted to be cost-effective (versus afatinib therapy). This was likely due to the difference in pricing of TKIs in Hong Kong and China.

The *EGFR* testing-guided use of TKI has been reported to be cost-effective in the literature when individual TKI strategy is compared with empirical chemotherapy. In cost-effectiveness analyses on *EGFR*-testing guided afatinib (in China) and erlotinib (in South Korea) versus empirical use of first-line chemotherapy, *EGFR*-mutation guided TKIs are reported to be cost-effective strategies.[4,5] In the present study, we showed consistent cost-effective acceptance of *EGFR*-mutation guided erlotinib and afatinib therapies versus empirical chemotherapy. *EGFR*-testing guided erlotinib therapy was the preferred cost-effective strategy in Hong Kong.

There are some limitations to the present study. The model simplified real-life events of advanced NSCLC therapy. We included SAEs of TKI and chemotherapy, yet the impact of less SAEs were not fully represented. Only English-language publications were included, but relevant findings reported in other language (such as Chinese language) were not included in the present model. Loss of productivity was not included and might therefore underestimate the impact of NSCLC treatment on indirect cost.

Conclusion

EGFR mutation-guided use of afatinib, erlotinib, and gefitinib appear to gain higher QALYs than empirical chemotherapy (without *EGFR* mutation testing). *EGFR* mutation-guided erlotinib therapy seems to be the most cost-effective from the perspective of public healthcare provider in Hong Kong.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15160531). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. You JHS, Cho WCS, Ming WK, et al. *EGFR* mutation-guided use of afatinib, erlotinib and gefitinib for advanced non-small-cell lung cancer in Hong Kong: a cost-effectiveness analysis. PLoS One 2021;16:e0247860.

Acknowledgements

We thank Dr Kwok-hung Au for site supervision and Ms Leann Au for data retrieval at Queen Elizabeth Hospital, and Dr Wai-kit Ming for data retrieval at United Christian Hospital, literature search for model building, and data collection and analysis.

References

1. Hospital Authority. Overview of Hong Kong cancer statistics of 2017. Available from: https://www3.ha.org.hk/cancereg/pdf/overview/Summary%20of%20CanStat%202017.pdf.
2. National Comprehensive Cancer Network Clinical Practice Guideline in Oncology (NCCN Guidelines) Non-small cell lung cancer. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
3. Gu X, Zhang Q, Chu YB, et al. Cost-effectiveness of afatinib, gefitinib, erlotinib and pemetrexed-based chemotherapy as first-line treatments for advanced non-small cell lung cancer in China. Lung Cancer 2019;127:84-89.
4. You R, Liu J, Wu DB, et al. Cost-effectiveness analysis of *EGFR* mutation testing and afatinib versus gemcitabine-cisplatin as first-line therapy for advanced non-small-cell lung cancer in China. Cancer Manag Res 2019;11:10239-48.
5. Lim EA, Lee H, Bae E, Lim J, Shin YK, Choi SE. Economic evaluation of companion diagnostic testing for *EGFR* mutations and first-line targeted therapy in advanced non-small cell lung cancer patients in South Korea. PLoS One 2016;11:e0160155.