TYROSINE KINASE INHIBITORS AS FIRST LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER (WITH LOCAL ECONOMIC EVALUATION)

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DISCLAIMER
Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and/or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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DISCLOSURE

The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia
EXECUTIVE SUMMARY

Introduction

In Malaysia, lung cancer is among the most common cancers among males, accounts for 16.3% of all cancers in male and third most common cancer in the general population. The age-standardised rate (ASR) for male was 14.7 per 100,000 population and 5.6 per 100,000 for female.

Remarkably, increasing evidence has been accumulated to strongly support predictive role of epidermal growth factor receptor (EGFR) gene mutation in non-small cell lung cancer (NSCLC) patients treated with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). As a result, EGFR inhibition strategy, which was originally limited to patients failed from previously standard treatment, has been used as first-line strategy in NSCLC patients potentially benefiting from the treatment of EGFR-TKIs.

This technology review was conducted following a request by a Senior Oncology Consultant from National Cancer Institute to review the safety, efficacy/effectiveness and cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer. Decision analytic modelling was also performed based on available local data to determine the cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer and to explore the uncertainty that may provide useful information for policy makers including for price negotiation.

Objective/aim

The objectives of this systematic review were to assess the safety and efficacy/effectiveness and cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer as well as to conduct local economic evaluation of these drugs based on available data.

Results and conclusions

From the systematic search, 26 titles were identified to be possibly related to the topic. Among those titles, ten studies were excluded due to ineligible population/patient groups, using TKI as second-line and maintenance therapy as well as different comparators used for evaluation. As the result, three meta analysis, one health technology assessment report, eight multicentres, open label, randomised controlled trials, one cross sectional study and three economic evaluation studies included in this review.
Based on the above review, there were fair to good level of retrievable evidence with low to moderate risk of bias to suggest that Erlotinib and Gefitinib significantly prolonged progression free survival but not overall survival and increased overall response rates when compared with standard chemotherapy in the previously untreated advanced non-small cells lung cancer patients with epidermal growth factor receptor (EGFR) gene mutation.

From the decision analytic modelling that has been conducted, the deterministic incremental cost-effectiveness ratio (ICER) of Erlotinib and Gefitinib is RM298, 904.98 and RM261, 898.27 respectively. The price of tyrosine kinase inhibitors, duration of progression free and number of patients who responded to the treatment have shown to be a sensitive parameter for ICER and may be a key determinant before considering the first line treatment for advanced non-small cell lung cancer for EGFR mutation positive patient. From the sensitivity analysis, it was found that reduction of drug price up to 75% demonstrated a potential cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer in patient with EGFR mutation positive based on suggested cost-effectiveness value by WHO.

Methods


Google Scholar was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 4th March 2015.
1. INTRODUCTION

In Malaysia, lung cancer is among the most common cancers among males, accounts for 16.3% of all cancers in male and third most common cancer in the general population. The age-standardised rate (ASR) for male was 14.7 per 100,000 population and 5.6 per 100,000 for female. The incidence was more than twice higher among males when compared to females. Chinese were found to have higher incidence rate compared to Malay and Indian. The incidence of lung cancer increased with age and it is reported in 2007 that the peak of age-specific incidence rate was within 70-75 age groups. Lung cancer is diagnosed at an advanced stage in majority of patients, which is the primary reason behind the high mortality rate associated with this disease. The National Cancer Registry of Malaysia report in 2007 stated that 60% of the lung cancer cases were detected at stage IV and only 12% of the cases were firstly diagnosed at stage I and II.

Non-small cell lung cancer (NSCLC) accounts for nearly 80% to 85% of all cases of lung cancer, which can be further classified into three histological sub-types of adenocarcinoma, squamous cell carcinoma and large-cell undifferentiated carcinoma. Since most of the patients were diagnosed at an advanced stage (IIIB or IV), systematic platinum-based doublet chemotherapy remains the standard care despite marginal improvement in survival.

Epidermal growth factor receptor (EGFR)-dependent pathway plays an important role in the development and progression of human epithelial cancers, including NSCLC. EGFR mutation has been confirmed as predictors of efficacy for EGFR-tyrosine kinase inhibitors (EGFR-TKIs). Gefitinib and erlotinib are two similarly small, orally active, selective and reversible EGFR-TKIs molecules, which have been extensively used in NSCLC. Remarkably, increasing evidence has been accumulated to strongly support predictive role of EGFR gene mutation in NSCLC patients treated with EGFR-TKIs. As a result, EGFR inhibition strategy, which was originally limited to patients failed from previously standard treatment, has been used as first-line strategy in NSCLC patients potentially benefiting from the treatment of EGFR-TKIs.

The Protocol for Systemic Therapy of Cancer is being revise by multidisciplinary healthcare providers in Malaysia and these Tyrosine
Kinase Inhibitors are to be considered as first line treatment for NSCLC patients with these criteria:

- Stage IIIb and IV adenocarcinoma
- EGFR mutation positive for exon 19 deletion
- Performance status 0-2
- Never or ex-smoker

In this group of patients, TKI must only be prescribed by either an oncologist or oncology trained respiratory physician.

This technology review was conducted following a request by a Senior Oncology Consultant from National Cancer Institute to review the safety, efficacy/effectiveness and cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer. Decision analytic modelling was also performed based on available local data to determine the cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer and to explore the uncertainty that may provide useful information for policy makers including for price negotiation.

2. OBJECTIVE / AIM

The objectives of this systematic review were to assess the safety and efficacy/effectiveness and cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer as well as to conduct local economic evaluation of these drugs based on available data.

3. TECHNICAL FEATURES

The development of Erlotinib and Gefitinib has been led by the discovery of 4-anilinoquinazolines, which was discovered to exhibit epidermal growth factor receptor (EGFR) inhibitory activity. These tyrosine kinase inhibitors block the signal pathways involved in the cell proliferation, resulting in slow growth of the tumor.

Gefitinib has received a United Kingdom marketing authorisation for treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations. Similarly, Erlotinib also has received marketing authorisation for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations.

The recommended daily oral dosage of Gefitinib is 250mg/day. Meanwhile, Erlotinib is recommended to be given orally as 150mg/day and
dosage reductions are possible to 100mg or 50mg/day.⁶ Both treatments were given to selected patients until the disease progressed.

4. METHODS

4.1. Searching


Google Scholar was used to search for additional web-based materials and information. No other limits were applied. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 4th March 2015. Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

**Inclusion criteria:**

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults with advanced non-small cell lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Comparators</td>
<td>1) Best supportive care</td>
</tr>
<tr>
<td></td>
<td>2) Single agent chemotherapy</td>
</tr>
<tr>
<td></td>
<td>3) Platinum-based chemotherapy</td>
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</table>
| Outcomes          | 1) Progression-free survival  
|                  | 2) Overall survival  
|                  | 3) Response rates  
|                  | 4) Adverse effects  
|                  | 5) Health-related quality of life  
|                  | 6) Incremental cost-effectiveness ratio (ICER)  

| Study design                  | Health Technology Assessment, Systematic Reviews, Randomised Controlled Trial (RCT), Non Randomised Controlled Trial, Cohort studies, Cross sectional studies,  

| Language                | English full text articles  

**Exclusion criteria:**

| Study design | Studies conducted in animals, narrative reviews, case series, case reports, commentary, letters  
| Interventions | Gefitinib or Erlotinib as second-line treatment or maintenance therapy  
| Comparator    | Placebo, Tyrosine Kinase Inhibitor, Recombinant Monoclonal Antibody  
| Language      | Non English full text articles  

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and graded according to US/Canadian preventive services task force (Appendix 2). Data were extracted and summarised in evidence table as in Appendix 3.

5. **RESULTS AND DISCUSSION**

From the systematic search, 26 titles were identified to be possibly related to the topic. Among those titles, ten studies were excluded due to ineligible population/patient groups, using TKI as second-line and maintenance therapy as well as different comparators used for evaluation. As the result, three meta analysis, one health technology assessment report, eight multicentres, open label, randomised controlled trials, one cross sectional study and three economic evaluation studies included in this review.
5.1. Safety

Results from the systematic review showed that the common adverse events with tyrosine kinase inhibitors (TKI) were diarrhea, rash, acne, dry skin and pruritis.\textsuperscript{3,4,7,8} Erlotinib-related rash were reported in 1021 (82%) patients of any grade with 36% of the patients experienced grade 0 to 1 while 46% had grade 2 to 4 rash.\textsuperscript{9} In addition, it has also been reported that liver enzyme elevations were also seen in Erlotinib and Gefitinib groups. Interstitial lung disease is also known as EGFR-TKI related lethal disease, however, less than 1% of patients treated with TKI would develop the interstitial lung disease.\textsuperscript{3}

5.2. Efficacy/Effectiveness

When considering the outcomes of various chemotherapeutic options for treatment of patients with NSCLC, most of the literatures concerning the effectiveness in terms of progression free survival (PFS), response rates, overall survival and health-related quality of life. Although Erlotinib and Gefitinib belong to the same group, most studies on these drugs were conducted separately. Therefore, the efficacy and effectiveness of these two TKIs will be discussed separately in this review.

5.2.1 Erlotinib

Three meta-analyses of two Erlotinib trials were retrieved from the scientific databases search. These analyses included a multicentre open label randomised cross over phase III trial European Tarceva versus Chemotherapy (EURTAC) and multicentre open label randomised phase III trial (OPTIMAL) involving 349 patients of stage IIIB and IV with presence of EGFR mutations from European region and China respectively. The primary endpoint of these trials was progression free survival with secondary endpoints of response rate and overall survival.

A. Progression free survival

Among 173 patients in EURTAC trial, the median progression free survival (PFS) was 9.7 months (95%CI; 8.4 to 12.3) in Erlotinib group and 5.2 months (95% CI; 4.4 to 5.8) \textit{(HR} 0.37, 95%;\textit{CI} 0.25–0.54; \textit{p}<0.0001\textit{)} in standard chemotherapy group. There was a favourable hazard ratio for risk of progression in patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 1 treated with Erlotinib versus chemotherapy, (0.26, 95% CI; 0.12 to 0.59) and (0.37, 95%CI; 0.22 to 0.62) respectively.\textsuperscript{3}
Similarly, the OPTIMAL trial showed that treatment with Erlotinib was associated with longer PFS compared with chemotherapy. The median PFS for Erlotinib and chemotherapy was 13.1 months (95% CI; 10.58 to 16.53) and 4.6 months (95% CI; 4.21 to 5.42), (HR 0.16, 95% CI: 0.1 to 0.26; p<0.0001) respectively. The progression free survival was reported to be consistent irrespective of the performance status.  

Haaland et al conducted a meta analysis of first line therapies in advanced non-small cell lung cancer harbouring EGFR-activating mutations and a sub-analysis comparing Erlotinib and combination of chemotherapy. The author found that the pooled hazard ratio for progression free survival from the meta-estimates is 0.25 (95% CI; 0.15 to 0.42). Similar result was reported by Gao et al. with the pooled hazard ratio for progression-free survival was 0.26 (95% CI; 0.10 to 0.67). A substantial heterogeneity was reported between the randomised controlled trials.

B. Overall Survival

For secondary endpoints, the overall survival was found not to differ significantly with the median overall survival that has been reported was 19.3 months (95% CI; 14.7 to 26.8) in Erlotinib group and 19.5 months (95% CI; 16.1-not assessable) in chemotherapy group (HR 1.04, 95% CI; 0.65-1.68; p=0.87). These results was supported by findings from Haaland et al with a pooled hazard ratio of 1.06 (95% CI; 0.82 to 1.37). The overall survival data from these trials was without confirmatory results and has been suggested not to differ significantly between the two groups possibly related to the potential impact of crossover treatment.

Mok et al reported that median overall survival was reported as 11.5 months (95% CI; 7.6 to 14.3). A further analysis also showed that median overall survival for patients with Erlotinib-related rash of grade 2 to 4 was 19.5 months (95% CI; 17.8 to 21.1) versus 12.2 months (95% CI; 10.6 to 13.6) for patients with grade 0 to 1 rash.

C. Overall Response Rate

The overall response rate in Erlotinib group was 67% and 15% in chemotherapy group in EURTAC trial and the overall response rate in OPTIMAL trial for was 83% for Erlotinib group and 36% for chemotherapy group.
Haaland et al reported that the pooled odds ratio for overall response rate was 8.2 (95% CI; 4.5 to 15.1). This result was found to be consistent with the findings from another meta analysis by Liang et al. which showed that the pooled odds ratio for overall response rate was 8.23 (95% CI; 4.88 to 13.88). It was also reported by Gao et al. that there was a statistically significant difference in the overall response rate between Erlotinib and chemotherapy with the pooled relative risk of 11.99 (95% CI; 6.80 to 21.15; p<0.001).

Based on an observation by Mok et al, the tumor response rate in those who received Erlotinib as first line treatment was 31%.

### 5.2.2 Gefitinib

Two meta-analyses on the effectiveness of Gefitinib were included in this review. These two analyses involved four multicenter, randomised controlled trials of patients with NSCLC, which will be explained in further details. Apart from that, two studies on quality of life for patients receiving Gefitinib were also included.

The Iressa Pan-Asia Study (IPASS) was an open-label trial comparing Gefitinib with carboplatin plus paclitaxel. A total of 1217 advanced NSCLC patients were recruited from 87 centers in Hong Kong, China, Indonesia, Japan, Malaysia, the Philippines, Singapore Taiwan and Thailand with approximately 51% Chinese and 19% Japanese, among others. The analysis population included 609 Gefitinib treated patients and 608 carboplatin plus paclitaxel treated patients. The primary end-point was progression free survival while the secondary end-points were overall survival, objective response rate, quality of life, reduction in symptoms, safety and adverse-event profile.

Another study by Maemondo et al was a multicenter Japanese trial comparing Gefitinib with carboplatin plus paclitaxel in active EGFR mutation patient population, also known as NEJ002 trial. A total of 230 EGFR mutation positive NSCLC patients were recruited at 43 institutions in Japan from 2006 to 2009. The analysis was based on 114 patients in each treatment arm. The primary end-point was progression free survival and the secondary end-points included overall survival, response rate and toxic effects.

The West Japan Thoracic Oncology Group Study (WJTOG 3405) was an open-label trial comparing Gefitinib with cisplatin plus docetaxel combination chemotherapy in EGFR mutation enriched patient population. A total of 177 EGFR mutation positive patients were recruited from 36 centers in Japan from 2006 to 2009. The efficacy analysis was based on 86 patients in Gefitinib group and 86 patients
receiving cisplatin/docetaxel. The primary end-point was progression free survival. The secondary end-points were overall survival and response rate. The tertiary end-points were disease control rate, safety and mutation-type-specific survival.

The First-SIGNAL study was a multicenter, open-label, phase III trial comparing Gefitinib with gemcitabine plus cisplatin in never-smokers with advanced NSCLC stage IIIB/IV whereby the EGFR mutation status were unknown in the beginning of the randomisation. A total of 313 patients were recruited from 3 major hospitals in Korea. The efficacy analysis was based on 159 patients in Gefitinib group and 150 patients in gemcitabine/cisplatin group. Fifty-three patients in Gefitinib group and 43 patients in chemotherapy group were eligible for subgroup analysis of enriched EGFR mutation. The primary end-point was overall survival while the secondary end-points were progression free survival, response rate and quality of life.

### A. Progression free survival

In the IPASS trial by Mok et al, the median progression free survival (PFS) for overall study population was significantly longer in Gefitinib group compared to carboplatin/paclitaxel group (HR = 0.74; 95%CI 0.65 to 0.85; P<0.001). Subgroup analysis of 261 patients with EGFR mutation positive also demonstrated a similar result which favoured Gefitinib (HR = 0.48; 95%CI 0.36 to 0.64; P<0.001). However, in the subgroup of 176 patients with EGFR mutation negative, PFS was significantly longer among those who received carboplatin/paclitaxel (HR = 2.85; 95%CI 2.05 to 3.98; P<0.001).

Similarly, NEJ002 trial also showed that the median PFS was significantly longer in the Gefitinib group (10.8 months vs 5.4 months) than in the carboplatin/paclitaxel group (HR = 0.30; 95%CI 0.22 to 0.41; P<0.001).

In the WJTOG 3405 study, PFS was significantly longer in the Gefitinib group than in the docetaxel/cisplatin group, with a median PFS time of 9.2 months compared with 6.3 months and a hazard ratio of 0.489 (95%CI 0.336 to 0.710; log-rank p<0.0001).

In the First-SIGNAL study by Han et al, there was no significant difference in terms of PFS between Gefitinib and combination of gemcitabine/cisplatin in overall study population (5.8 months vs 6.4 months, HR = 1.198; 95%CI 0.944 to 1.520; P= 0.138). However, subgroup analysis among patients receiving Gefitinib demonstrated that the patients with EGFR mutation positive had longer PFS
compared to those without EGFR mutation (HR = 0.377; 95%CI 0.210 to 0.674; P<0.001).  

Two meta-analyses on the effectiveness of Gefitinib conducted by Gao et al and Haaland et al included the above four multicenter trials. However, the meta-analysis by Gao et al included the unpublished, preliminary report of First-SIGNAL study that was presented by Lee Jin Soo, one of the co-author of the trial, during 13th World Conference on Lung Cancer in 2009. Nonetheless, both meta-analyses demonstrated a similar pooled hazard ratio for the median PFS. Gao et al found that patients receiving Gefitinib have a longer progression free survival with the pooled hazard ratio of 0.43 (95%CI; 0.32 to 0.58) from the meta-estimates. This result was found to be consistent with the findings from the most recent meta-analysis by Haaland et al (pooled HR = 0.44; 95%CI; 0.31 to 0.63).  

B. Overall Survival

Overall survival was defined consistently across the four trials as “time from randomisation to death from any cause”. Hazard ratios from individual studies showed no significant difference for overall survival between Gefitinib and different doublet platinum-based chemotherapies.  

These findings were supported by the pooled hazard ratios obtained from the two meta-analyses. Pooled hazard ratio from Gao et al was 0.97 (95%CI; 0.78 to1.20) while the meta-estimate of pooled HR for overall survival in Haaland et al was 0.99 (95%CI; 0.81 to1.21).  

C. Overall Response Rate

Three of the multicenter trials (IPASS, NEJ002 and WJTOG 3405) assessed objective or overall response rate (ORR) as the secondary end-point and all trials reported significantly higher ORR in the Gefitinib group compared to chemotherapy group (P<0.001). In First-SIGNAL trial, ORR were similar in both groups (55.4% vs 46.0%; P= 0.101).  

Both meta-analyses proved that the ORR was significantly higher in patients with EGFR positive treated with Gefitinib compared to chemotherapy. The pooled odds ratios meta-estimates from Gao et al and Haaland et al were 3.82 (95%CI; 2.28 to 6.39) and 4.1 (95%CI; 2.7 to 6.3) respectively.
D. Health-related quality of life

Two studies discussed on the quality of life of NSCLC patients receiving Gefitinib as first-line treatment. The paper by Thongprasert et al was an extension from IPASS, whereby the evaluation of health-related quality of life (HRQoL) and symptoms improvement were pre-planned secondary objectives for the overall population and posthoc analyses for EGFR mutation subgroups in the study.\textsuperscript{14} The rates of improvement in terms of quality of life (QoL) were assessed using Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaires and Trial Outcome Index (TOI) while symptoms improvement was measured using the Lung Cancer Subscale (LCS) domain of the FACT-L. The study demonstrated that the rates of improvement in QoL and symptoms for patients with EGFR mutation positive significantly favoured Gefitinib over carboplatin/paclitaxel:\textsuperscript{14}

- FACT-L total score 70.2\% versus 44.5\%; odds ratio (OR) = 3.01; 95\%CI 1.79 to 5.07; p<0.001
- TOI score 70.2\% versus 8.3\%; OR = 3.96; 95\%CI 2.33 to 6.71; p<0.001
- LCS domain 75.6\% versus 53.9\%; OR = 2.70; 95\%CI 1.58 to 4.62; p<0.001

Conversely, for patients with EGFR mutation negative, the improvement in QoL and symptoms significantly favoured carboplatin/paclitaxel over Gefitinib:\textsuperscript{14}

- FACT-L total score 14.6\% versus 36.3\%; OR 0.31; 95\%CI 0.15 to 0.65; p=0.002
- TOI score 12.4\% versus 28.8\%; OR 0.35; 95\%CI 0.16 to 0.79; p=0.011
- LCS domain 20.2\% versus 47.5\%; OR 0.28; 95\%CI 0.14 to 0.55; p<0.001

Another study by Oizumi et al was an extension from NEJ002 trial with the objective to conduct QoL analysis as the secondary end-point for the clinical trial.\textsuperscript{15} Level I The Care Notebook which was a set of self-administered and cancer-specific questionnaire was used to assess QoL. There were 3 major scales in this questionnaire, namely physical well-being, mental well-being and life well-being. From the evaluation, there was significant improvement in QoL for patients receiving Gefitinib in 2 domains, physical well being (p<0.0001) and life well-being (p<0.0001). However, no significant difference between the two treatments in mental well-being (p=0.458).\textsuperscript{15} Level I
5.3. Cost/Cost-effectiveness

Wang et al. conducted a cost utility analysis from the perspective of Chinese healthcare system to evaluate the cost effectiveness between Erlotinib and carboplatin-gemcitabine in patients with advanced EGFR mutation-positive NSCLC and found that Erlotinib yielded lower cost and lower QALY compared with chemotherapy. The total costs discounted at 3% per year and QALYs for Erlotinib and chemotherapy were (USD 40,107.95, 1.4) and (USD 88,227.30, 1.96) respectively.\(^\text{16}\)

In agreement with this, another cost utility analysis by Chouaid et al. from French healthcare system perspective also reported that first line Erlotinib followed by chemotherapy after progression also yielded lower cost and lower QALY compared with the reverse strategy in fit elderly patients with advanced NSCLC. The total costs and QALYs for Erlotinib followed by chemotherapy and reverse strategy were (€27,724, 0.51) and (€31,688, 0.52) respectively. The limitation of this analysis is that the EGFR status of patient is unknown.\(^\text{17}\)

However, these two analyses used data of overall quality adjusted life years which may suggest the reason for low effectiveness in Erlotinib group. This is because the model predicted that the patients in Erlotinib group have higher risk of death after disease progression and the EGFR status of the patient is unknown.\(^\text{16,17}\)

As for Gefitinib, a cost utility analysis modelled from 3 landmark studies (IPASS, NEJ002 and WJTOG 3405) was performed to compare the cost-effectiveness of EGFR mutation testing and first-line treatment with Gefitinib for advanced lung adenocarcinoma patients with standard practice in Singapore health facilities.\(^\text{18}\) The standard practice or Strategy 1 was "No EGFR mutation testing, first-line treatment with chemotherapy, second-line treatment with Gefitinib followed by best supporting care (BSC)". Alternatively, Strategy 2 consisted of “EGFR mutation testing and first-line treatment with Gefitinib followed by second-line chemotherapy (for patients with activating EGFR mutations) or chemotherapy followed by best supporting care, BSC (for those without EGFR mutation)". Based on the model, it was found that Strategy 2 was a dominant strategy compared to standard practice with a total QALYs increased by 0.04 and costs decreased by SGD 2400. Sensitivity analysis demonstrated that EGFR testing followed by first line Gefitinib for patients with active mutation compared to no testing followed by chemotherapy alone produced an incremental cost of SGD 20,600 and incremental QALYs of 0.27, which yielded an incremental cost-effectiveness ratio (ICER) of SGD 77,160 per QALY gained. The analysis also found that Gefitinib was not cost-effective in treatment of patients without EGFR mutations with ICER between SGD 129,000 and SGD 196,000 per QALY gained.\(^\text{18}\)
Brown et al performed a cost utility analysis as part of health technology assessment on first-line chemotherapy for patients with locally advanced or metastatic NSCLC which include Gefitinib. Based on the decision analytic model from the UK National Health Services (NHS) and Personal Social Services perspectives conducted on the same 3 landmark studies, the ICER for Gefitinib versus Carboplatin/paclitaxel was £55,605 per QALY gained, while the ICER for Gefitinib versus Docetaxel/cisplatin was £30,483 per QALY gained. It was concluded that the cost-effectiveness results were not generally favourable for Gefitinib, which generates base-case ICERs in excess of £50,000 per QALY gained when compared to third generation chemotherapy doublets namely Paclitaxel and Docetaxel.
5.4 Decision Analytic Model

5.4.1. Methods

A decision tree model was developed to estimate the cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer with positive EGFR mutation using Microsoft Excel 2007. This model was selected based on the suitability of the timeline and availability of the data. This type of decision analytic model had also been used in other cost-effectiveness analysis for various study objectives in NSCLC patients. The interventions being compared in this model are Gefitinib or Erlotinib and standard chemotherapy.

Clinical experts were consulted to identify the most suitable and representative clinical pathways. The decision tree model is illustrated as Figure 1 with the simulated clinical pathways as follow:

1) Tyrosine Kinase Inhibitors followed by 4 cycles of chemotherapy after disease progression and subsequently best supportive care for those who respond
2) Non responder will received Tyrosine Kinase Inhibitors for 1 month followed by 4 cycles of chemotherapy and subsequently best supportive care
3) Patient who progressed after 4 cycles of chemotherapy received 4 cycles of second line chemotherapy and subsequently best supportive care
4) Non responder to chemotherapy received best supportive care after 1 cycle of first line and second line of chemotherapy.

The clinical parameters were extracted from OPTIMAL trial and used in this analysis on the basis that Chinese had the highest incidence rate among all ethnicity in Malaysia. Therefore; the points of estimate from this trial were selected to be used in this analysis. Median survival was selected as the distribution of survival time was normally skewed. It was used as the estimation for duration of progression free. The estimated maximum duration of survival among patients with stable disease with NSCLC was extracted from a study by Maemondo et al and was used as the time horizon. Other data such as percentage of NSCLC among lung cancer, proportion of stage IIIIB and IV patients and proportion of EGFR mutation positive were derived from local studies and data available in Malaysian Cancer Registry.

The costs used in this analysis were based on the published literature using local data and also from Ministry of Health Malaysia and were estimated using the perspective of the health care provider (Table 1). The costs included in this analysis were cost of investigations, cost of
drugs and cost of procedures such as specialist clinics, admissions and follow-ups.\textsuperscript{26} A discount rate of 3\% was applied for costs and effectiveness as recommended in the Pharmacoeconomic Guidelines for Malaysia.\textsuperscript{20} The costs derived from different year were adjusted to costs of the year 2014.

The outcomes presented as quality adjusted life years (QALY) which was calculated by multiplying the health states utilities with the duration spent under each treatment. However, in absence of local health states utilities data for NSCLC, the UK health states utilities for NSCLC were used to derive the quality adjusted life years.\textsuperscript{18,28} Similar sources of utilities have also been used in a cost utility analysis by Permsuwan et al.\textsuperscript{21}

Deterministic sensitivity analysis was performed as one way sensitivity analysis to determine the parameter uncertainty. All results were presented as incremental cost-effectiveness ratio (ICER) per QALY gained.

Table 1: Cost of medical services and drugs

<table>
<thead>
<tr>
<th>Medical services/drug cost</th>
<th>Point of estimate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib tablet 150mg (30’s/pack)</td>
<td>RM5,319.99</td>
<td>Ministry of Health (Malaysia)</td>
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<tr>
<td>Gefitinib tablet 250mg (30’s/pack)</td>
<td>RM4,493.45</td>
<td>Ministry of Health (Malaysia)</td>
</tr>
<tr>
<td>Standard chemotherapy (per cycle)</td>
<td>RM 11,131.27</td>
<td>Al Junid SM et al.\textsuperscript{26} (Malaysia)</td>
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<tr>
<td>Best supportive care (per month)</td>
<td>RM634.17</td>
<td>Dranitaris G et al.\textsuperscript{27} (Malaysia)</td>
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<td>EGFR mutation test (per test)</td>
<td>RM1,173</td>
<td>Ministry of Health (Malaysia)</td>
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<tr>
<td>Outpatient clinic (per visit)</td>
<td>RM303.02</td>
<td>Ezat SW et al.\textsuperscript{25} (Malaysia)</td>
</tr>
</tbody>
</table>
Figure 1: Decision tree model

Advanced non-small cell lung cancer with EGFR mutation positive

TKI

Response (Progression Free) → Disease Progression → Die

No response → Disease Progression → Die

stable disease

Chemotherapy

Response (Progression Free) → Disease Progression → Die

No response → Disease Progression → Die

stable disease

stable disease
5.4.2. Assumptions

In absence of required data, it is a common approach to use assumptions based on available published literature or experts’ consultations. The following assumptions were used in this economic model:

1) All health states are mutually exclusive; the patient will not be in other health states while in one particular health state.

2) Similar clinical benefits and health states utilities were used for patients who received tyrosine kinase inhibitors as there was insufficient evidence to suggest a difference in clinical benefits between Erlotinib and Gefitinib. Therefore, the model focus on the differential cost between the tyrosine kinase inhibitors.

3) All patients with stage III and IV NSCLC were offered an EGFR mutation testing as it has been suggested that EGFR mutations are the most important factor in the progression free survival benefit.

4) Best supportive care was offered to all patients after failure of second line treatment.

5) Non responder of chemotherapy received 1 cycle of first line chemotherapy and 1 cycle of second line chemotherapy.

6) Non responder of tyrosine kinase inhibitors received 4 cycles of chemotherapy and subsequently best supportive care.

7) Patient who progressed after responding to tyrosine kinase inhibitors received 4 cycles of chemotherapy and subsequently best supportive care.

8) Patient who progressed after responding to first line chemotherapy received 4 cycles of second line chemotherapy and subsequently best supportive care.

9) The cost of lung cancer management per patient per year was assumed as equal to 4 cycles of chemotherapy treatment per year regardless of the chemotherapy combination.
5.4.3. Results

The results reflected the ICER per QALY gained if tyrosine kinase inhibitors were recommended as first line treatment for advanced non-small cell lung cancer with positive EGFR mutation. The deterministic incremental cost-effectiveness ratio (ICER) of Erlotinib and Gefitinib is RM298, 904.98 and RM261, 898.27 per QALY gained respectively. These results were significantly higher than the suggested value of cost-effectiveness by WHO, between 1-3 times gross domestic product (GDP) per capita. However, these results were based on a model with time horizon of approximately 30 months which may not fully reflect the long term effectiveness of the treatment. It may potentially be used as a reference for the decision maker to assist in the negotiation and reimbursement policy making processes based on the short term effectiveness.

5.4.4. Sensitivity analysis

One way sensitivity analysis was conducted to determine which parameters affect the ICER by varying the value of the clinical parameters and costs. These results showed that by varying the cost between 50%-75%, the ICER was extremely reduced for both Erlotinib and Gefitinib. The price reduction of Erlotinib resulted with an ICER between RM120, 260.90 to RM179, 808.93 per QALY gained. Similarly, the price reduction of Gefitinib also resulted with a lower ICER between RM111, 009.23 to RM160, 941.47 per QALY gained. These values may potentially be used as a reference in decision making process for wider accessibility based on the healthcare provider’s affordability.

Other parameters such as duration of progression free survival and increased number of patient who responded to tyrosine kinase inhibitors were also among the sensitive factors in this model as progression free survival were longer in tyrosine kinase inhibitor groups compared with standard chemotherapy. The ICER yielded by varying the lower and upper range of progression free survival were RM344, 482.33 and RM259, 790.87 for Erlotinib while Gefitinib yielded an ICER of RM303,554.72 and RM226,487.27 respectively. With the increase of response rate by 10%, the ICER were RM259,423.53 for Erlotinib and RM222,265.53 for Gefitinib. In contrast, the lower response rate increased the ICER of Erlotinib and Gefitinib to RM345,793.60 and RM308,966.57 respectively.

In view of lower health utilities experienced by the patients with rash, the ICER for this group of patients is slightly higher than the base case; RM339,271.89 for Erlotinib and RM297,267.45 for Gefitinib. The health utilities of patient with rash is being explored in the analysis as rash was the most frequently reported adverse effects associated with tyrosine
kinase inhibitors. This would imply that adverse events may affect the quality of life of the patients who received tyrosine kinase inhibitors.

5.5 Limitations

This technology review has several limitations. Firstly, this review has been prioritized to include only Gefitinib and Erlotinib despite a variety of tyrosine kinase inhibitors available in the market. Secondly, studies comparing tyrosine kinase inhibitors with various combination of chemotherapy were included in this review. However, there was no study comparing Erlotinib with Gefitinib that was included in this review as the direct comparison was not the objective of this review. Moreover, it has been suggested that there was insufficient evidence to demonstrate any clinical benefits differences between Erlotinib and Gefitinib.

Although there was no restriction in language during the search, only English full text articles were included in this report.

In terms of the local economic evaluation, although every effort has been made in retrieving local data as model parameters, some of the values were not locally available. Thus, the most suitable parameters were carefully selected either based on the representativeness of the population or the availability of data within the Asia region. Several assumptions have been used based on the available literature and experts consultations.

6. CONCLUSION

Based on the above review, there were fair to good level of retrievable evidence with low to moderate risk of bias to suggest that Erlotinib and Gefitinib significantly prolonged progression free survival but not overall survival and increased overall response rates when compared with standard chemotherapy in the previously untreated advanced non-small cells lung cancer patients with epidermal growth factor receptor (EGFR) gene mutation.

From the decision analytic modelling that has been conducted, the price of tyrosine kinase inhibitors, duration of progression free and number of patients who responded to the treatment have shown to be a sensitive parameter for ICER and may be a key determinant before considering the first line treatment for advanced non-small cell lung cancer for EGFR mutation positive patient. From the sensitivity analysis, it was found that reduction of drug price up to 75% demonstrated a potential cost-effectiveness of tyrosine kinase inhibitors as first line treatment for advanced non-small cell lung cancer in patient with EFGR mutation positive based on suggested cost-effectiveness value by WHO.
7. REFERENCES


22. Zainal Ariffin O, Zainudin MA, Nor Saleha IT. Malaysian Cancer Statistics-Data and Figure Peninsular Malaysia National Cancer Registry Ministry of Health Malaysia; 2006.


8. **APPENDIX**

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

<table>
<thead>
<tr>
<th>Ovid MEDLINE® In-process &amp; Other Non-Index ted citations and</th>
<th>OvidMEDLINE® 1946 to present</th>
</tr>
</thead>
</table>

1. exp Carcinoma, Non-Small-Cell Lung/or exp Lung Neoplasms/
2. cancer$ or neoplas$ adj1 pulmonary.tw.
3. cancer$ or neoplasm$ adj1 lung.tw.
4. cancer of the lung.tw.
5. cancer of lung.tw.
6. non small cell lung adj1 carcinom$.tw.
7. non small cell lung cancer.tw.
8. lung carcinom$ adj non small cell.tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Protein Kinase Inhibitors/ or tyrosine kinase inhibitor.mp.
11. protein kinase adj inhibito$.tw.
12. kinase inhibitors protein.tw.
14. Tarceva.tw
15. Gefitinib.tw.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 9 AND 17
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<th><strong>EBM Reviews - Cochrane Central Register of Controlled Trials</strong></th>
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<td><strong>EBM Reviews - Health Technology Assessment</strong></td>
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<td><strong>EBM Reviews – Database of Abstracts of Reviews Effects</strong></td>
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<td><strong>EMBASE</strong></td>
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</table>
8.2. Appendix 2

DESIGNATION OF LEVELS OF EVIDENCE

I  Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III  Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris S2001)
**Appendix 3**

### Evidence Table: Safety

**Question**: Is Erlotinib and Gefitinib safe as first line treatment for advanced non-small cell lung cancer?

<table>
<thead>
<tr>
<th>Bibliographic citation</th>
<th>Study Type / Methodology</th>
<th>LE</th>
<th>Number of patients and patient characteristics</th>
<th>Intervention</th>
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<th>Outcome measures/ Effect size</th>
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<tbody>
<tr>
<td>Haaland B, Tan PS, de Castro GJ. et al.</td>
<td>Meta analysis of first line therapies in advanced non-small cell lung cancer harbouring EGFR-activating mutations. Journal of Thoracic Oncology. [online]. (2014); 9(6):805-811.</td>
<td>I</td>
<td>Sub analysis- Erlotinib Two phase III randomised controlled trial (OPTIMAL and EURTAC) of EGFR-mutated population (total number of 349 patients) Gefitinib Four phase III RCTs (IPASS, West Japan, NEJ002, First-SIGNAL) of EGFR-mutated patients (total number of 703 patients)</td>
<td>Erlotinib 1. Erlotinib 2. Gefitinib</td>
<td>Common adverse events with tyrosine kinase inhibitors were diarrhea, rash or acne, dry skin and pruritis. It has also been reported that liver enzyme elevation is also seen in erlotinib and gefitinib group.</td>
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<tr>
<td>Bibliographic citation</td>
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Two phase II randomised controlled trial (OPTIMAL and EURTAC) of EGFR-mutated population (total number of 349 patients)
**Gefitinib**
Four phase II RCTs (IPASS, West Japan, NEJ002, First-SIGNAL) of EFGR-mutated patients (total number of 703 patients) | Erlotinib
Gefitinib | Gemcitabine+ Carboplatin
Standard platinum-based doublet chemotherapy | - | Diarrhea and rash were more frequent in the EGFR-TKI group compared with chemotherapy
Less than 1% of patients treated with TKI would develop the interstitial lung disease. | - |
**Evidence Table**: Safety  
**Question**: Is Erlotinib a safe first line treatment for advanced non-small cell lung cancer?

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<td>Mok T, Wu YL, Au JS. et al. Efficacy and safety of Erlotinib in 1242 east/South East Asian Patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology.[online]. (2010);5(10):1609-1615.</td>
<td>Phase IV, open label single arm study.</td>
<td>II-3</td>
<td>1242 patients recruited within East/South-East Asian region (China, Taiwan, Hong Kong, Korea, Thailand, Malaysia and Indonesia). The patients received Erlotinib either as first, second or third line.</td>
<td>Erlotinib</td>
<td>-</td>
<td>Until disease progression, unacceptable toxicity or death</td>
<td>Erlotinib-related rash were reported in 1021 (82%) patients of any grade. 36% of the patients experienced grade 0 to 1 while 46% had grade 2 to 4 rash. 532 (435) of patients had one or more adverse events patients</td>
<td>-</td>
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<td>Bibliographic citation</td>
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<tr>
<td>Rosell R, Carcereny E, Gervais R. et al. Erlotinib versus standard chemotherapy as first line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. The Lancet. [online]. (2012); 13:239-246.</td>
<td>Multicentre, open-label, randomised, cross over phase 3 trial at 42 hospitals in France, Italy, and Spain.</td>
<td>1</td>
<td>174 patients:- -age older than 18 years -histological diagnosis of stage IIIB (with pleural effusion) or stage IV NSCLC (based on the sixth TNM staging system) -presence of activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21) -no history of chemotherapy for metastatic disease</td>
<td>Erlotinib</td>
<td>Standard platinum-based doublet chemotherapy</td>
<td>-</td>
<td>The median progression free survival (PFS) was 9.7 months (95%CI; 8.4 to 12.3) in Erlotinib group and 5.2 months (95% CI; 4.4 to 5.8) in standard chemotherapy group (HR 0.37,95% CI 0.25−0.54; p&lt;0.0001). The median overall survival was19.3 months (95% CI; 14.7 to 26.8) in Erlotinib group and 19.5 months (95%CI; 16.1-not assessable) in chemotherapy group (HR 1.04, 95%CI; 0.65−1.68; p=0.87)</td>
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Evidence Table  | Efficacy/Effectiveness
---|---
Question  | Is Erlotinib effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first line treatment for patients with advanced EGFR mutation-positive non-small-cell-lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 trial at 22 centres in China. The Lancet. [online].(2011);12:735-742.</td>
<td>Multicentre, open-label, randomised, phase 3 trial at 22 centres in China.</td>
<td>I</td>
<td>165 patients older than 18 years with histologically confirmed stage IIIB or IV NSCLC and a confirmed activating mutation of EGFR (exon 19 deletion or exon 21 L858R point mutation</td>
<td>Erlotinib</td>
<td>Gemcitabine+ Carboplatin</td>
<td>-</td>
<td>The median PFS for Erlotinib and chemotherapy was 13.1 months (95% CI; 10.58 to 16.53) and 4.6 months (95%CI; 4.21 to 5.42) respectively. An overall response rate were reported as 83% (68/82) for erlotinib and 36% (26/72) for chemotherapy (p&lt;0.0001)</td>
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</table>
### Evidence Table: Efficacy/Effectiveness

**Question**: Is Erlotinib effective as first line treatment for advanced non-small cell lung cancer?

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<td>Meta analysis of first line therapies in advanced non-small cell lung cancer harbouring EGFR-activating mutations</td>
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<td>Sub analysis- Two phase III randomised controlled trial of EGFR-mutated population. The included trials were OPTIMAL and EURTAC with total number of 349 patients.</td>
<td>Erlotinib</td>
<td>Gemcitabine+ Carboplatin Standard platinum-based doublet chemotherapy</td>
<td>-</td>
<td>The pooled hazard ratio for progression free survival and overall survival from meta-estimates are 0.25 (95%CI; 0.15 to 0.42) and 1.06 (95%CI; 0.82 to 1.37) respectively. The pooled odds ratio for overall response rate is 8.2 (95%CI; 4.5 to 15.1) There was no information of the consistency of these results.</td>
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<td>Gao G, Ren S,Li A et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomised controlled trials. International Journal of Cancer,[online]. (2011). Doi 10.1002/ijc.27396.</td>
<td>Meta analysis</td>
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<td>Erlotinib</td>
<td>Gemcitabine+ Carboplatin Standard platinum-based doublet chemotherapy</td>
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<td>The pooled hazard ratio for progression-free survival is 0.26, (95% CI; 0.10 to 0.67) with reported substantial heterogeneity between the trials,(I² =88.4%,p=0.003). There was a statistically significant difference in the overall response rate between Erlotinib and chemotherapy with the pooled relative risk of 11.99, (95% CI; 6.80 to 21.15; p&lt;0.001.) No pooled hazard ratio for overall survival presented in this trial.</td>
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## Evidence Table: Efficacy/effectiveness

### Question
Is Erlotinib effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Liang W, Wu X, Fang W. et al. Network meta-analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in patients with advanced non-small cell lung cancer harbouring EGFR mutations. PLOS One. [online] (2014);9(2).e85245. doi:10.1371/journal.pone.0085245.</td>
<td>Meta analysis</td>
<td>I</td>
<td>Direct meta analysis of two randomised controlled trial from EURTAC and OPTIMAL with total number of 349 patients.</td>
<td>Erlotinib</td>
<td>Gemcitabine+ Carboplatin Standard platinum-based doublet chemotherapy</td>
<td>-</td>
<td>The pooled odds ratio for overall response rate is 8.23 (95%CI:4.88 to 13.88) with low heterogeneity between the trials</td>
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</table>
**EvidenceTable** : Efficacy/effectiveness

**Question** : Is Erlotinib effective as first line treatment for advanced non-small cell lung cancer?

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<td>1242 patients recruited within East/South-East Asian region (China, Taiwan, Hong Kong, Korea, Thailand, Malaysia and Indonesia). The patients received Erlotinib either as first, second or third line.</td>
<td>Erlotinib</td>
<td>-</td>
<td>Until disease progression, unacceptable toxicity or death</td>
<td>Tumor response rate in those who received Erlotinib as first line treatment was 31% and median overall survival reported as 11.5 months (95%CI; 7.6 to 14.3).</td>
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<td>Haaland B, Tan PS, de Castro GJ, et al.</td>
<td>Meta analysis of first line therapies in advanced non-small cell lung cancer harbouring EGFR activating mutations</td>
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<td>Sub analysis- Four phase III randomised controlled trial of EGFR-mutated population. The trials included are - IPASS - West Japan - NEJ002 - First-SIGNAL</td>
<td>Gefitinib</td>
<td>IPASS – carboplatin + paclitaxel West Japan – cisplatin + docetaxel North-East Japan 002 – carboplatin + paclitaxel First-SIGNAL – gemcitabine + cisplatin</td>
<td>-</td>
<td>The pooled hazard ratio for progression free survival and overall survival from meta-estimates are 0.44 (95%CI; 0.31 to 0.63) and 0.99 (95%CI; 0.81 to 1.21) respectively. The pooled odds ratio for overall response rate is 4.1 (95%CI; 2.7 to 6.3) and for disease control rate is 2.1 (95%CI 1.3 to 3.5). Test of heterogeneity ($I^2$): PFS = 69% OS = 0% ORR = 32% DCR = 24%</td>
<td>Conclusion : Gefitinib out-performed chemotherapy in terms of progression-free survival, overall response rate and disease control rate</td>
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## Evidence Table: Efficacy/Effectiveness

### Question: Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?

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<td>Meta analysis</td>
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<td>Sub analysis- Four phase III randomised controlled trial of EGFR-mutated population. The trials included are - IPASS - West Japan - NEJ002 - First-SIGNAL Total number of patients = 703</td>
<td>Gefitinib</td>
<td>Mok et al (IPASS) – carboplatin + paclitaxel Mitsudomi et al (West Japan) – cisplatin + docetaxel Maemondo et al (NEJ 002) – carboplatin + paclitaxel Lee et al (First-SIGNAL) – gemcitabine + cisplatin</td>
<td>-</td>
<td>The pooled hazard ratio for progression free survival and overall survival from meta-estimates are 0.43 (95%CI; 0.32 to 0.58) and 0.97 (95%CI; 0.78 to1.20) respectively. The pooled odds ratio for overall response rate is 3.82 (95%CI; 2.28 to 6.39) Test of heterogeneity ($I^2$): PFS = 57.8% OS = 0% ORR = 54.6% Conclusion: The EGFR-TKI regimen significantly prolonged PFS and increased ORR when compared with platinum-based doublet chemotherapy in the previously untreated advanced NSCLC patients with EGFR mutation</td>
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**Evidence Table** : Efficacy/Effectiveness

**Question** : Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009 Sep 3;361(10):947-57. doi:10.1056/NEJMoa0810699. (IPASS)</td>
<td>Phase III, open-label, randomised – controlled trial Iressa Pan-Asia Study (IPASS) 87 centers in Hong Kong, China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan and Thailand.</td>
<td>I</td>
<td>Untreated patients in East Asia with advanced pulmonary adenocarcinoma, non-smokers or former light smokers. Gefitinib – 609 pt Carboplatin + paclitaxel – 608 pt Subgroup analysis for EGFR mutation : 437 patients sample (261 EGFR +ve, 177 EGFR –ve)</td>
<td>Gefitinib</td>
<td>carboplatin + paclitaxel</td>
<td>-</td>
<td>1. Progression free survival - overall : hazard ratio 0.74; 95%CI 0.65 to 0.85; P&lt;0.001 - EGFR mutation +ve : hazard ratio 0.48; 95%CI 0.36 to 0.64; P&lt;0.001 - EGFR mutation –ve : hazard ratio 2.85; 95%CI 2.05 to 3.98; P&lt;0.001 2. Objective response rate - overall : odds ratio 1.59; 95%CI 1.25 to 2.01; P&lt;0.001 - EGFR mutation +ve : higher in gefitinib group (P&lt;0.001) 3. Overall survival - overall: hazard ratio 0.91; 95%CI 0.76 to 1.10 - EGFR mutation +ve : hazard ratio 0.78; 95%CI 0.50 to 1.20 4. Quality of life (using FACT-L and TOI) - gefitinib group had a clinically relevant improvement in QoL • FACT-L score : OR 1.34; 95%CI 1.06 to 1.69 • TOI score : OR 1.78; 95%CI 1.40 to 2.26 Conclusion : first-line therapy with gefitinib as compared with carboplatin–paclitaxel prolongs PFS, increases the ORR, and improves quality of life among clinically selected patients with non–small-cell lung cancer.</td>
<td>Astra-Zeneca sponsored ITT</td>
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<td>Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010 Jun 24;362(25):2380-8. doi: 10.1056/NEJMoa0909530. (NEJ 002)</td>
<td>Multicenter, randomized, phase III trial</td>
<td>I</td>
<td>Advanced NSCLC with EGFR mutations positive. No history of previous chemotherapy. Gefitinib = 114 pts Chemotherapy = 114 patients</td>
<td>Gefitinib</td>
<td>Carboplatin + paclitaxel</td>
<td>-</td>
<td>1. Progression free survival - median duration 10.8 months vs 5.4 months - hazard ratio 0.30; 95%CI 0.22 to 0.41; P&lt;0.001 2. Objective response rate - higher in gefitinib group (73.7% vs 30.7%, P&lt;0.001 3. Overall survival - median survival time 30.5 months vs 23.6 months - not significant (P= 0.31) - hazard ratio not given.</td>
<td>Grants from the Japan Society for Promotion of Science and the Japanese Foundation for the Multidisciplinary Treatment of Cancer ITT</td>
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</table>

**Conclusion:**
The efficacy of first-line gefitinib was superior to that of standard chemotherapy, with acceptable toxicity, in patients with advanced non–small-cell lung cancer harbouring sensitive EGFR mutations. Selection of patients on the basis of EGFR-mutation status is strongly recommended.
**Evidence Table**: Efficacy/Effectiveness

**Question**: Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Mitsudomi T, Morita S, Yatabe Y et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010 Feb;11(2):121-8. doi: 10.1016/S1470-2045(09)70364-X. (West Japan or WJTOG 3405)</td>
<td>Multicenter, randomized, open-label, phase III trial 36 centres in Japan</td>
<td>I</td>
<td>Advanced NSCLC with EGFR mutations positive. - include post-operative recurrence. - chemotherapy naive OR - if post-operative recurrence patients received adjuvant chemotherapy, the interval between the last chemo and registration for study exceeded 6 months for platinum-doublet and 1 month for oral tegafur+uracil Gefitinib = 86 pts Chemotherapy = 86 pts</td>
<td>Gefitinib</td>
<td>Cisplatin + docetaxel</td>
<td>18 months (follow-up still ongoing)</td>
<td>1. Progression free survival - median duration 9.2 months vs 6.3 months - hazard ratio 0.489; 95%CI 0.336 to 0.710; P&lt;0.0001 2. Objective response rate - higher in gefitinib group (62.1% vs 32.2%, P&lt;0.0001 3. Overall survival - immature data, follow-up still ongoing - hazard ratio 1.638; 95%CI 0.7 to 3.58.</td>
<td>Fund: West Japan Oncology Group (WJOG), non-profit organisation ITT</td>
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### Evidence Table: Efficacy/Effectiveness

#### Question: Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?

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</table>
| Han JY, Park K, Kim SW, et al. First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol. 2012;30(10):1122–8. (First-SIGNAL) | Multicenter, randomized, open-label, phase III trial | I | Advanced NSCLC stage IIIB/IV - EGFR mutation status unknown in the beginning of the randomisation | Gefitinib | Gemcitabine + cisplatin - *given for up to a maximum of 9 cycles (standard protocol is 4 to 6 cycles) | Median: 35 months (19.3 to 49.4 months) | 1. Overall survival - median duration 22.3 months vs 22.9 months - OS not significantly different between the two treatment arms (hazard ratio 0.932; 95%CI 0.716 to 1.213; P = 0.604)  
2. Progression free survival - median duration 5.8 months vs 6.4 months - no significant difference (hazard ratio 1.198; 95%CI 0.944 to 1.520; P= 0.138) - subgroup analysis gefitinib group (EGFR +ve vs EGFR –ve) : HR 0.377; 95%CI 0.210 to 0.674.  
3. Response rate - similar in both groups (55.4% vs 46.0%, P = 0.101) | Research funding by AstraZeneca (partly by National Cancer Center Grants) ITT | Gefitinib versus standard gemcitabine + cisplatin chemotherapy in never-smokers NSCLC patients. EGFR mutation testing is needed to optimize patient selection for first-line gefitinib. |

*ITT = Intent to treat.*
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<td>1. The rates of improvement in FACT-L total score, TOI and LCS for patients with EGFR mutation positive significantly favoured gefitinib over carboplatin/paclitaxel. - FACT-L total score 70.2% vs 44.5%; OR 3.01; 95%CI 1.79 to 5.07; p&lt;0.001 - TOI 70.2% vs 8.3%; OR 3.96; 95%CI 2.33 to 6.71; p&lt;0.001 - LCS 75.6% vs 53.9%; OR 2.70; 95%CI 1.58 to 4.62; p&lt;0.001</td>
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<td>2. For patients with EGFR mutation negative significantly favoured carboplatin/paclitaxel over gefitinib. - FACT-L total score 14.6% vs 36.3%; OR 0.31; 95%CI 0.15 to 0.65; p=0.002 - TOI 12.4% vs 28.8%; OR 0.35; 95%CI 0.16 to 0.79; p=0.011 - LCS 20.2% vs 47.5%; OR 0.28; 95%CI 0.14 to 0.55; p&lt;0.001</td>
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<td>Conclusion: Patients with EGFR mutation positive had greater improvement in HRQoL and symptoms improvement when treated with gefitinib. Conversely, those with EGFR mutation negative benefited most from carboplatin/paclitaxel, which highlighting the importance of personalized NSCLC treatment based on tumor molecular characteristics.</td>
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Evidence Table: Efficacy/Effectiveness

Question: Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?
### Evidence Table: Efficacy/Effectiveness

**Question**: Is Gefitinib effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Oizumi, S., Kobayashi, K., Inoue, A., et al. (2012). Quality of Life with Gefitinib in Patients with EGFR-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial. The Oncologist, 17, 863–870. (extension from NEJ 002)</td>
<td>Multicenter, randomized, phase III trial</td>
<td>I</td>
<td>Advanced NSCLC with EGFR mutations positive. No history of previous chemotherapy. Gefitinib = 114 pts Chemotherapy = 110 patients Pt returning QoL booklet: - gefitinib 81 pts (71%) - chemo 82 pts (75%) Complete data: - gefitinib 72 pts (63%) - chemo 76 pts (69%)</td>
<td>Gefitinib</td>
<td>Carboplatin + paclitaxel</td>
<td>-</td>
<td>Hazard ratio 1. Patients who received gefitinib had a significantly longer time to deterioration than patients who received carboplatin-paclitaxel: - for pain and SOB (HR 0.28; 95%CI 0.17 to 0.46) - for daily functioning (HR 0.2; 95%CI 0.17 to 0.59) - for anxiety (HR 0.44; 95%CI 0.22 to 0.87) 2. Significant improvement in QoL for patients receiving gefitinib in 2 domains: physical well-being (p&lt;0.0001) and life well-being (p&lt;0.0001). No significant difference between the two treatments in mental well-being (p=0.458)</td>
<td>Grants from the Japan Society for Promotion of Science and the Japanese Foundation for the Multidisciplinary Treatment of Cancer ITT</td>
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**Evidence Table**: Economic evaluation

**Question**: Is Erlotinib cost-effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>Wang S, Peng L, Li J. et al. A Trial-based cost-effectiveness analysis of Erlotinib alone versus Platinum-based doublet chemotherapy as first-line therapy for Eastern Asian nonsquamous non-small cell lung cancer. PLOS One.[online].(2013);8(3):e55917.doi:10.1371/journal.pone.0055917</td>
<td>Cost-effectiveness analysis</td>
<td>-</td>
<td>Data was based from a multicentre OPTIMAL trial conducted at 22 centres in China</td>
<td>150mg/day Erlotinib</td>
<td>Carboplatin-gemcitabine chemotherapy (carboplatin administered intravenously under AUC=5 on day 1, and gemcitabine administered intravenously at 1000mg/m² on day 1 and 8 for 4 cycles</td>
<td>10 years time horizon</td>
<td>The intervention yielded lower costs and lower QALY compared with chemotherapy. The total costs discounted at 3% per year and QALYs for Erlotinib and chemotherapy was (USD 40,107.9, 1.4) and (USD 88,227.30, 1.96) respectively.</td>
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**Evidence Table:** Economic evaluation

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<tr>
<td>Chouaid C, Le Haer C, Locher C. et al. Cost – effectiveness of Erlotinib versus chemotherapy for first-line treatment of non-small cell lung cancer (NSCLC) in fit elderly patients participating in a prospective phase 2 study (GFPC 0504). BMC Cancer.[online].(2012); 12:301</td>
<td>Cost-effectiveness analysis</td>
<td>-</td>
<td>Between July 2006 AND November 2008, 22 centres enrolled 100 patients to a multicenter, open label randomised phase II trial with mean age of 76 years old.</td>
<td>Erlotinib followed after progression, by weekly chemotherapy (docetaxel 30mg/m² for 6 consecutive weeks and gemcitabine 900mg/m² at weeks 1,2,4 and 5, followed by a two week treatment-free period)</td>
<td>Weekly chemotherapy (docetaxel 30mg/m² for 6 consecutive weeks and gemcitabine 900mg/m² at weeks 1,2,4 and 5, followed after progression with Erlotinib, followed by a two week treatment-free period.</td>
<td>Until death or the last date of patient known to be alive</td>
<td>The intervention yielded lower costs and lower QALY compared with the reverse strategy. The total costs and QALYs for Erlotinib and chemotherapy was (€27,724, 0.51) and (€31,688, 0.52) respectively. The base case incremental cost-effectiveness ratio was €395,400/QALY.</td>
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Evidence Table: Economic evaluation
Question: Is Gefitinib cost-effective as first line treatment for advanced non-small cell lung cancer?

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<tr>
<td>De Lima Lopes G, Segel JE, Tan DSW, et al. Cost-effectiveness of epidermal growth factor receptor mutation testing and first-line treatment with gefitinib for patients with advanced adenocarcinoma of the lung. Cancer. 2012;118(4):1032–9.</td>
<td>Cost-utility analysis (CUA)</td>
<td>3</td>
<td>3 studies included (IPASS, NEJ 002 and West Japan)</td>
<td>* Refer to decision tree Strategy 2</td>
<td>* Refer to decision tree Strategy 1</td>
<td>Based on median PFS and overall survival from landmark studies.</td>
<td>Results: 1. Primary analysis: - Strategy 2 is a dominant strategy compared to standard practice with a total QALYs increase by 0.04 and costs decreased by SGD 2400. 2. Scenario testing: - EGFR testing followed by first line gefitinib for patients with active mutation VS no testing followed by chemotherapy alone: incremental cost and QALYs to be SGD 20,600 and 0.27, yielded an ICER of SGD 77,160 per QALY gained. 3. Gefitinib was not cost-effective in treatment of patients without EGFR mutations (ICER between SGD 129,000 and SGD 196,000 per QALY gained)</td>
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<td>- Decision analytic model (decision tree)</td>
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<td>EGFR mutation testing and first-line treatment with gefitinib followed by second-line chemotherapy (for patients with activating EGFR mutations) AND Chemotherapy followed by best supporting care, BSC (for those without EGFR mutation)</td>
<td>No EGFR mutation testing, first-line treatment with chemotherapy, second-line treatment with gefitinib followed by best supporting care (BSC)</td>
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<td>- Perspectives: patients and/or government payers (Singapore)</td>
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<td>- outcome data obtained from 3 landmark studies for gefitinib (IPASS, NEJ 002, West Japan)</td>
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<td>- cost based on 3 cancer centres in Singapore, using 2010 Singapore dollars (SGD)</td>
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<td>- Health related utility values estimated from an economic model by Nafees et al.</td>
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<td>- sensitivity analysis: one-way SA and scenario based SA</td>
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<td>- Results in cost per QALY gained.</td>
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(dose and cycles not mentioned)

Conclusion:
1. Mutation testing and first-line therapy with gefitinib for patients with activating EGFR mutations and chemotherapy for those without is a dominant strategy compared with no testing followed by first-line chemotherapy and second-line gefitinib for all unselected patients with lung adenocarcinoma.

2. First-line treatment with gefitinib is dominant compared to chemotherapy in the initial treatment of patients with activating mutations.

3. Gefitinib does not seem to be cost-effective in the treatment of patients without activating EGFR mutations.
**Evidence Table**: Economic evaluation  
**Question**: Is Gefitinib cost-effective as first line treatment for advanced non-small cell lung cancer?

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- cost-utility analysis (CUA) of studies with epidermal growth factor receptor (EGFR) mutation-positive population  
- cost based on BNF and eMIT (electronic market information tools)  
- Health related utility values were estimated from an economic model by Nafees et al.  
- Decision analytic model from the UK NHS and Personal Social Services perspectives.  
- ICER determined through deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA).  
- outcomes of interest : cost per QALY gained. | 3 studies included (IPASS, NEJ002 and West Japan) | Gefitinib 250mg/day, orally. | 1. Carboplatin + paclitaxel (carboplatin administered intravenously under AUC=5 on day 1, and paclitaxel administered intravenously at 175mg/m² on day 1 for 4 cycles of) (IPASS and NEJ002)  
2. Docetaxel + cisplatin (both administered intravenously at 75mg/m² on day 1 for 4 cycles) (West Japan) | 1. ICER for Gefitinib vs Carboplatin + paclitaxel  
- DSA : £54,911 per QALY gained  
- PSA : £55,605 per QALY gained  
2. ICER for Gefitinib vs Docetaxel + cisplatin  
- DSA : £29,553 per QALY gained  
- PSA : £30,438 per QALY gained | 1. 21 days in one cycle |

**Conclusion**:  
The cost-effectiveness results are not generally favourable for gefitinib, which generates base-case ICERs in excess of £50,000 per QALY gained. The CE results achieve ICERs <£30,000 per QALY only when clinical evidence is restricted to the smallest of the three RCTs included.