ORIGINAL ARTICLE

# Prognosis of Tyrosine Kinase Inhibitor Therapy for Non-Small Cell Lung Cancer

**Agus Andreas Santoso[1*], Suryanti Dwi Pratiwi[1], Yani Jane Sugiri[1], Harun Al Rasyid[2], Aditya Sri Listyoko[3]**

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[3]Doctoral Student, Division of Respiratory Medicine and Rheumatology, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori, Japan.

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**ABSTRACT**

**Introduction:** Non-small cell lung cancer (NSCLC) was the primary cause of death in lung cancer. Tyrosine kinase inhibitors (TKIs) were one of the management options for NSCLC. Meanwhile, serum carcinoembryonic antigen (CEA) plays a crucial role in the diagnosis and prognosis of NSCLC patients. This study aimed to determine the effectiveness of epidermal growth factor receptor (EGFR)-TKI based on progression-free survival (PFS) and overall survival (OS) in NSCLC patients with common EGFR mutations.

**Methods:** This retrospective cohort study used a total sampling method. The serum CEA level was measured before the initial treatment. Tyrosine kinase inhibitors therapy was monitored with PFS and OS. Statistical analysis for comparing prognosis in NSCLC among TKI groups used Kruskal-Wallis, analysis of variance (ANOVA), Mann-Whitney, and Spearman's rho tests. A significant analysis referred to a p-value of <0.05.

**Results:** The participants were 189 patients, consisting of 106 on gefitinib, 43 on erlotinib, and 40 on afatinib. The average PFS values in the gefitinib, erlotinib, and afatinib groups were 9.9±5.25, 8.77±4.53, and 12.83±7.02 months, respectively (p=0.016). Furthermore, there were no significant OS among the gefitinib (14.91±7.61 months), erlotinib (14.54±7.64 months), and afatinib group (15.51±8.13 months, p=0.867). There was a significant correlation between CEA levels and PFS (r=0.146; p=0.046) and between CEA levels and OS (r=0.223; p=0.004).

**Conclusion:** Although afatinib may prolong PFS compared with gefitinib and erlotinib, it did not significantly impact OS. Increased serum CEA levels before treatment significantly improved PFS and OS. However, elevated CEA levels are usually associated with a poor prognosis in NSCLC.

## INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of death in the world, especially in industrialized countries. It was found in 80-85% of all lung cancer cases, including squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.[1] The prevalence of NSCLC throughout the world is 85% of all lung cancers, while in Indonesia, NSCLC is the number one cause of death caused by cancer (13.2%).[2,3]

Epidermal growth factor receptor (EGFR) mutations were mutations in transmembrane receptors on the cell surface in NSCLC patients.[4] The prevalence of EGFR in Asia was 51.4% among 1,450 patients based on the PIONEER study.[5] Moreover, the frequency of EGFR mutations was elevated for patients of East Asian ethnicities, especially Vietnamese (64.2%), Thai (53.8%), Chinese (51.8%), and Filipino (50.0%).[6] Epidermal growth factor receptor mutations were categorized into common and uncommon mutations. The common EGFR mutation refers to mutations in exon 19 and 21 (especially L858R), whereas the uncommon EGFR mutation refers to exon 18 (G719A, C, or S in G719X), exon 20 (T790M), and exon 21

*Corresponding author: agus.andreas.0125@gmail.com

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(L861Q).[7]

Management of NSCLC, apart from chemotherapy, involves several types of cancer drugs with targeted therapy, particularly EGFR-tyrosine kinase inhibitors (TKIs). Meanwhile, EGFR-TKIs were commonly used as first-line treatments for NSCLC in Indonesia, including gefitinib and erlotinib as first-generation agents and afatinib as a second-generation agent.[8] Afatinib was more effective in prolonging progression-free survival (PFS), reflecting its broader inhibition profile and potential to delay possible resistance mechanisms compared to first-generation EGFR-TKIs.[9] However, it did not provide additional overall survival (OS) benefits.[9]

Several serum tumor markers are available for NSCLC that may be useful for risk stratification, early detection, selection of optimal therapy, prognosis assessment, and monitoring of recurrence, particularly carcinoembryonic antigen (CEA) levels. Moreover, serum CEA level is one of the most studied and validated serum markers in NSCLC. Furthermore, serum CEA levels were typically elevated in NSCLC patients, ranging from 35-70% at diagnosis, primarily in the adenocarcinoma subtype that harbored an EGFR mutation and in the advanced setting.[10] Serum CEA levels might be used as a prognostic factor or asses of management in NSCLC patients.[11] The elevated serum CEA levels were associated with metastatic and increased mortality rates in NSCLC patients.[11]

In Indonesia, first-line therapy for NSCLC with common EGFR mutations was usually treated with TKI first- and second-generation agents, especially gefitinib, erlotinib, and afatinib. Therefore, this study investigated the prognostic significance of comparing patients treated with TKI therapy using PFS and OS. Moreover, this study also investigated the correlation between serum CEA levels and prognosis outcomes (mainly PFS and OS) after beginning TKI therapy. Several previous studies have shown that serum CEA levels may predict prognosis in NSCLC with common EGFR mutations.[11,12]

## METHODS

This retrospective cohort study was conducted according to the electronic health records of NSCLC patients. The number of participants was 189 NSCLC patients collected from January 2016 to December 2019 using a total sampling method. This study was approved by the Health Research Ethics Committee of Dr. Saiful Anwar General Hospital, Malang, Indonesia (No.400/233/K.3/302/2020). Eligible participants provided written informed consent.

The study procedure involved participants diagnosed with NSCLC and common EGFR mutations, such as those in exon 19 (insertions/deletions) and exon 21 (L858R). The participants received EGFR-TKI therapy, which is commonly used in Indonesia, typically consisting of gefitinib and erlotinib as first-generation agents, and afatinib as a second-generation agent. The participants had complete electronic health records, which required several data points to be available, especially CEA levels, disease progression, and therapy outcomes (such as PFS and OS). Furthermore, patients who could not be monitored according to medical records and whose lung cancer metastasized to other organs were excluded from this study.

Carcinoembryonic antigen was a monomeric oncofetal glycoprotein expressed during embryonic and fetal development. Its levels were measured to evaluate CEA levels in the bloodstream, the most common marker of NSCLC. Moreover, normal CEA levels were defined as <5.0 ng/mL, and >5.0 ng/mL were considered elevated CEA levels.[12] The CEA levels were determined using a peripheral blood sample (5 mL) collected and measured before the initial treatment via a sequential chemiluminescent immunoassay.

Progression-free survival and OS in this study determined the prognosis of NSCLC after therapy with EGFR-TKI. Progression-free survival refers to the duration a patient lives without worsening disease from the beginning of diagnosis or treatment, which is to be evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[13] Meanwhile, OS is defined as the time from the initiation of diagnosis or treatment until death occurs.[4] The outcome measurements in this study were demonstrated in terms of duration (in months).

The participants were selected based on electronic health records in the hospital, which were identified according to the study criteria. Data was collected and coded into Microsoft Excel. Furthermore, the data entry and analysis were performed using Statistical Package for Social Sciences (SPSS) version 24.0. The average and median are described in numeric data, while categorical data are represented by frequency and percentage. The one-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used for PFS and OS analysis to compare EGFR-TKI groups based on the data distribution. The Mann-Whitney test was used to analyze the comparison between each EGFR-TKI group. The Spearman's rho test assessed the correlation between CEA levels and therapy response, primarily regarding PFS and OS. These statistical tests were also selected based on the data distribution. The statistical analysis was considered significant when $p<0.05$.

## RESULTS

### Characteristics of participants

In this study, 189 participants were enrolled, with 106 participants receiving gefitinib therapy, 43 receiving erlotinib therapy, and 40 receiving afatinib therapy. The majority of participants were females, with an estimated number of 105 (55.6%), of whom 58 participants received gefitinib (54.7%), 21 received erlotinib (48.8%), and 26 received afatinib (65%; p=0.323). Most of the participants had CEA levels in the higher category (143 participants, 75.7%) distributed as follows: gefitinib group with 80 participants (75.5%), erlotinib group with 30 participants (69.8%), and afatinib group with 33 participants (82.5%; p=0.401). Based on smoking status, the majority of participants were non-smokers, with 53.8% non-smokers in the gefitinib group, 51.2% non-smokers in the erlotinib group, and 65% non-smokers in the afatinib group, with p=0.383 (Table 1).

Based on CEA levels, patients receiving gefitinib therapy (24.5% had normal serum CEA values and 75.5% had elevated CEA), erlotinib therapy (30.2% had normal CEA and 69.8% had elevated CEA), and afatinib therapy (17.5% had normal CEA and 82.5% had elevated CEA). No significant differences were found between CEA levels and EGFR-TKI (p=0.401). Meanwhile, most participants had adenocarcinoma cancer cell types compared to adenosquamous carcinoma, with a comparison in the gefitinib group (94.3% adenocarcinoma and 5.7% adenosquamous carcinoma), erlotinib (97.7% adenocarcinoma and 2.3% adenosquamous carcinoma), and afatinib (90% adenocarcinoma and 10% adenosquamous carcinoma). The statistical test analysis results between cancer cell types and EGFR-TKI obtained p=0.327. There was no significant difference between EGFR mutation and EGFR-TKI (p=0.710), with the majority of participants having EGFR exon 19 (gefitinib of 53.8%, erlotinib of 60.5%, and afatinib of 52.5%) (Table 1).

**Table 1.** Characteristics of participants

| Variable | Gefitinib n (%) | Erlotinib n (%) | Afatinib n (%) | p |
|---|---|---|---|---|
| **Age (mean±SD)** | 57.82±10.46 | 57.74±9.65 | 61.45±9.75 | 0.132[a] |
| ≤40 years old | 7 (6.6) | 3 (7) | 0 (0) | 0.241[b] |
| >40 years old | 99 (93.4) | 93 (93) | 40 (100) | |
| **Sex** | | | | |
| Male | 48 (45.3) | 22 (51.2) | 14 (35) | 0.323[b] |
| Female | 58 (54.7) | 21 (48.8) | 26 (65) | |
| **Smoking** | | | | |
| No | 57 (53.8) | 22 (51.2) | 26 (65) | 0.383[b] |
| Yes | 49 (46.2) | 21 (48.8) | 14 (35) | |
| **CEA levels** | | | | |
| Normal | 26 (24.5) | 13 (30.2) | 7 (17.5) | 0.401[b] |
| High | 80 (75.5) | 30 (69.8) | 33 (82.5) | |
| **Cancer cell type** | | | | |
| Adenocarcinoma | 100 (94.3) | 42 (97.7) | 36 (90) | 0.327[b] |
| Adenosquamous carcinoma | 6 (5.7) | 1 (2.3) | 4 (10) | |
| **EGFR mutation** | | | | |
| EGFR exon 19 (ins/del) | 57 (53.8) | 26 (60.5) | 21 (52.5) | 0.710[b] |
| EGFR exon 21 (L858R) | 49 (46.2) | 17 (39.5) | 19 (47.5) | |

SD: standard deviation; CEA: carcinoembryonic antigen; EGFR: epidermal growth factor receptor; [a]Analysis of variance (ANOVA) test (normal distribution); [b]Chi-square test

### Prognosis of epidermal growth factor receptor-tyrosine kinase inhibitor therapy in non-small cell lung cancer patients

The mean PFS values in each group included gefitinib (9.9±5.25 months), erlotinib (8.77±4.53 months), and afatinib (12.83±7.02 months). There was a significant difference in PFS values among gefitinib, erlotinib, and afatinib (p=0.016). Comparison of PFS between each EGFR-TKI included gefitinib vs erlotinib (p=0.268), gefitinib vs afatinib (p=0.028), and erlotinib vs afatinib (p=0.005). Meanwhile, based on OS, there was no significant difference between gefitinib (14.91±7.61 months), erlotinib (14.54±7.64 months), and afatinib (15.51±8.13 months; p=0.867) (Table 2).

**Table 2.** Effectiveness of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy against non-small cell lung cancer with common EGFR mutations

| Drug Response | Gefitinib | Erlotinib | Afatinib | p |
|---|---|---|---|---|
| **PFS (n)** | 106 | 43 | 40 | |
| Mean±SD | 9.9 ± 5.25 | 8.77 ± 4.53 | 12.83 ± 7.02 | 0.016*[a] |
| Min-max | 2 – 24 | 1 – 25 | 3 – 31 | |
| **OS (n)** | 91 | 35 | 35 | |
| Mean±SD | 14.91 ± 7.61 | 14.54 ± 7.64 | 15.51 ± 8.13 | 0.867[b] |
| Min-max | 2 – 30 | 2 – 26 | 1 – 32 | |

PFS: progression-free survival; SD: standard deviation; Min: minimum; Max: maximum; OS: overall survival; [a]Kruskal-Wallis's test (non-normal distribution); [b]Analysis of variance (ANOVA) test (normal distribution); *Significant <0.05

### Correlation between serum carcinoembryonic antigen levels and response to therapy in non-small cell lung cancer patients

Serum CEA levels and PFS are significantly correlated, with statistical values indicating r=0.146 and p=0.046. Meanwhile, a significant correlation was also identified between serum CEA levels and OS, with r=0.223 and p=0.004 (Figure 1).

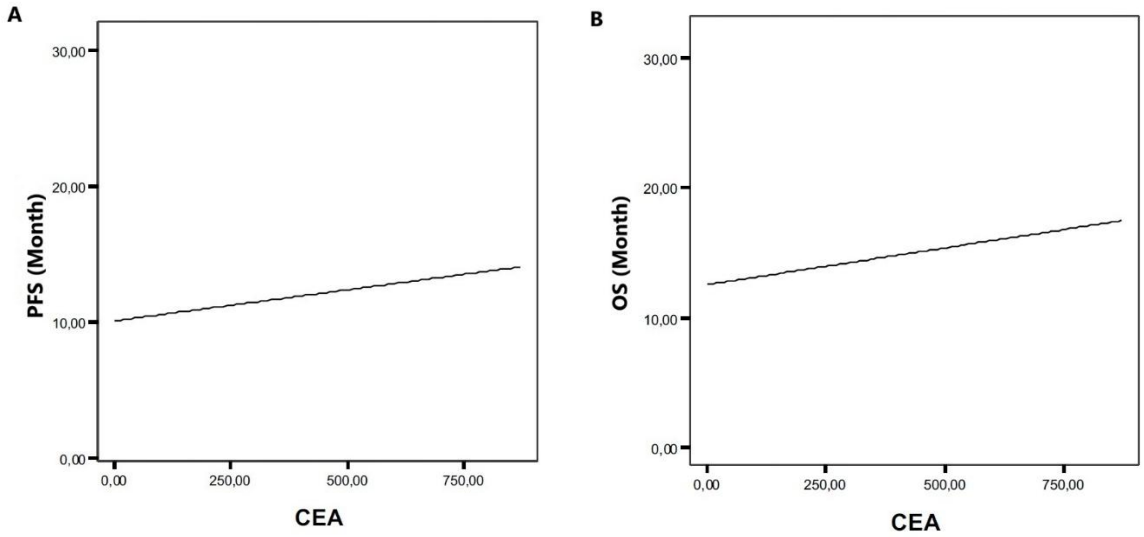


**Figure 1.** A) Significant correlation between carcinoembryonic antigen (CEA) and progression-free survival (r=0.146; p=0.046); B) A considerable correlation was also found between CEA and overall survival (r=0.223; p=0.004)

## DISCUSSION

In this study, the participants had an average age of 58.57±10.19 years old and were predominantly aged >40 years old. Non-small cell lung cancer cases occurring in individuals under 40 years of age were a small percentage (1-10%).[14] Moreover, the incidence of NSCLC increases significantly with age.[14] Another study, conducted from 2010 to 2017, also showed an increased incidence of NSCLC in older patients (over 65 years old) compared to younger patients (under 65 years old), at 31% and 69%, respectively.[15] Despite all incidences of NSCLC decreasing during this period, the incidence was markedly higher among older patients than among younger patients.[15]

In this study, most participants were females. Several previous studies reported that most NSCLC patients were males, and other studies also found that females were the most dominant.[16–18] Likewise, in Indonesia, there was no predominant sex in NSCLC cases.[3,4] Despite no difference in prevalence, females have a lower risk of death than males for treatment in NSCLC by 20%.[19]

Most participants in this study were not smokers. Abbas, *et al*. (2020) stated that smoking habits were associated with poor prognostic factors of PFS in NSCLC patients.[20] According to Shiels, *et al*. (2024), although lung cancer death rates declined in the last decade, the risk of lung cancer death was 86% less in never-smokers than in ever-smokers (especially former smokers, 78%, or current smokers, 92%).[21] Meanwhile, Zhu, *et al*. (2024) reported that patients with smoking cessation have significantly improved OS than patients with current smoking in all cancers.[22] In addition, Indonesia has the highest smoking prevalence among males worldwide, with >70% of males smoking.[3]

Most participants had elevated serum CEA levels, mainly in the gefitinib, erlotinib, and afatinib therapy groups. Among these markers of NSCLC, CEA is a sensitive and useful tumor marker for cancer diagnosis and therapy assessment.[23,24] Moreover, based on several previous studies, serum CEA levels were considered

normal when the value was <5 ng/mL.[23,25–27] Furthermore, 35 to 70% of NSCLC patients might have increased serum CEA levels at diagnosis.[10] Meanwhile, serum CEA levels may play a predictive role in the EGFR mutation status of NSCLC patients.[24]

The type of NSCLC was mostly adenocarcinoma cancer cells in the gefitinib, erlotinib, and afatinib therapy group. Lung cancer is classified into small cell lung cancer (SCLC) and NSCLC. Most lung cancer was NSCLC (80%).[28] Moreover, subtypes of NSCLC include adenocarcinoma (70%), squamous cell carcinoma (20%), and large cell carcinoma (10%), with adenocarcinoma the most common histological type.[29,30] According to Melosky, *et al*. (2022), most NSCLCs worldwide were adenocarcinomas, accounting for 73%.[16] In addition, the majority of participants in a previous study had a diagnosis of adenocarcinoma (94.9%).[5]

Most participants in the TKI therapy groups had an EGFR mutation in exon 19 (insertions/deletions). Melosky, *et al*. (2022) found that the prevalence of EGFR mutations was higher in Asia than in Western countries (34.8% and 14.4%, respectively).[16] Soo, *et al*. (2024) showed that a common EGFR mutation was mostly exon 19 insertions/deletions (48.5%) than exon 21 L858R (34%).[17] In Asia, the EGFR exon 19 mutation also has a higher incidence than the exon 21 L858R mutation, at 24.3% and 22.9%, respectively, in the 1,450 NSCLC cases.[5] A study in Indonesia reported that most NSCLC incidents were EGFR mutations in exon 19, which were identified using cytological specimens and circulating tumor deoxyribonucleic acid (ctDNA) methods of 30.6% and 19.4%, respectively.[4]

A significant comparison exists of the average PFS among patients treated with EGFR-TKI. The afatinib group had a higher average PFS than the gefitinib and erlotinib groups. Meanwhile, the average OS showed no statistically significant difference among gefitinib, erlotinib, and afatinib. When compared with gefitinib as a first-line treatment for NSCLC with EGFR mutations, afatinib was more effective in prolonging PFS, reflecting the broader inhibitory profile of afatinib and the potential to delay resistance mechanisms compared with first-generation EGFR-targeted therapies. However, it did not provide an additional OS benefit.[9,30]

There was a significant positive correlation between serum CEA levels and PFS and OS. This positive correlation indicates elevated serum CEA levels are associated with prolonged PFS and OS. Meanwhile, some previous studies found that increased serum CEA levels were associated with shortened PFS and OS.[20,27] On the other hand, other studies reported that patients treated with EGFR-TKI who had elevated pretreatment levels of CEA had a more prolonged survival and a better response than those with lower CEA levels.[27,31] Although this condition is similar to that in this study, serum CEA levels should be re-examined during treatment with EGFR-TKI to assess the prognosis of NSCLC patients.[10,24]

## CONCLUSION

Although afatinib may prolong PFS compared with gefitinib and erlotinib, it did not provide additional impact on OS in NSCLC patients. Measurement of CEA levels may suggest establishing a diagnosis and predicting prognosis in NSCLC patients, as its elevation is associated with a poorer prognosis. Despite a significant correlation between increasing serum CEA levels before treatment and improving PFS and OS, repeat CEA examinations during therapy should be monitored in future studies.

## LIMITATIONS OF THE STUDY

This study has several limitations, including measuring serum CEA levels only prior to the initial treatment and insufficient data to demonstrate the contribution of CEA in NSCLC. Additionally, comparison with other groups, such as those with uncommon NSCLC and double mutation, must be included.

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### Authors' Contributions
Data curation, funding acquisition, investigation, project administration, writing–original draft, writing–review and editing: AAS. Conceptualization, methodology, resources: SDP. Supervision, validation: YJS, ASL. Visualization: YJS. Formal analysis, investigation, software: HAR.

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