T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

by Laksmi Wulandari

Submission date: 08-Mar-2022 12:41PM (UTC+0800)
Submission ID: 1779167980
File name: culating_Tumor_DNA_LungIndia_2020_37_1_13_274414_dr_evin-2-7.pdf (1.04M)
Word count: 5205
Character count: 27108

Original Article

T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

Vinodini Merinda[1], Gatot Soegiarto[2], Laksmi Wulandari[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [2]Division of Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [3]Division of Thoracic Oncology, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

Background: Plasma circulating tumor deoxyribonucleic acid (ctDNA) test is an alternative method to detect the T790M mutation. Compared to conventional tumor rebiopsy, ctDNA possesses several advantages including less invasive, faster, lower costs, and having minimal risk of complications for patients. **Objective:** The main objective of the study is to identify the prevalence of T790M mutations in lung adenocarcinoma patients who progressed after tyrosine kinase inhibitors (TKIs) therapy using ctDNA examination. **Materials and Methods:** This was a retrospective cohort study based on medical records of lung adenocarcinoma patients in the Oncology Outpatient Clinic of Dr. Soetomo General Hospital within the period of January 2017–June 2018. Patients who progressed after receiving first-line epidermal growth factor receptor-TKI (EGFR-TKI) undergone plasma ctDNA examination and genotyping using digital platforms (Droplet Digital™ PCR) method. **Results:** In total, there were 39 patients who met the criteria for ctDNA testing. Thirty-three patients (84.6%) received first-line gefitinib, while the other six (15.4%) received erlotinib. The T790M mutations were detected in 46.2% of patients. In addition, EGFR common mutation in exon 19 and exon 21 were detected in 87.2% of patients. Median progression-free survival of patients receiving first-line gefitinib or erlotinib were both around 9 months and did not differ significantly. **Conclusions:** CtDNA examination successfully detected T790M mutation in a certain proportion of lung adenocarcinoma patients who progressed after first-line EGFR-TKI without the need for difficult and invasive rebiopsy.

KEY WORDS: T790M mutation, first-line epidermal growth factor receptor-tyrosine kinase inhibitors, lung adenocarcinoma,plasma circulating tumor deoxyribonucleic acid

Address for correspondence: Mrs. Laksmi Wulandari MD., PhD., FCCP, Division of Thoracic Oncology, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jl. Mayjen Prof. Dr. Moestopo No. 6-8, Surabaya 60285, Indonesia.
E-mail: laksmi.wulandari@fk.unair.ac.id

Received: 23-04-2019 **Revised:** 08-09-2019 **Accepted:** 12-10-2019 **Published:** 31-12-2019

INTRODUCTION

Lung cancer is one of the most common causes of cancer mortality in the United States. In 2018, the incidence of new lung cancer cases was estimated to be 234,030 (121,680 of men and 112,350 of women), and the mortality of lung cancer was estimated at 154,050 (83,550 of men and

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_182_19

How to cite this article: Merinda V, Soegiarto G, Wulandari L. T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors. Lung India 2020;37:13-8.

70,500 of women).[1] Nonsmall-cell lung cancer (NSCLC) is considered as the most common type, which comprised more than 85% of all lung cancer cases.[2] Adenocarcinoma is the most common type of lung cancer and is associated with the presence of epidermal growth factor receptor (EGFR) mutation in about 14%–19% of patients in the Western countries and in 40%–48% of patients in Asia.[3]

The EGFR-tyrosine kinase inhibitors (EGFR-TKI), including gefitinib, erlotinib, and afatinib, are recommended as the first-line treatment for patients with positive EGFR-mutation. Despite achieving notable efficacy from EGFR-TKI treatment, a majority of patients eventually develop resistance after a median progression-free survival (PFS) of approximately 1-year (8–14 months). The progressive disease could be accounted to different resistance mechanisms to TKI. The most common resistance mechanism (approximately 60%) is the T790M secondary mutation. Consequently, patients who progressed after receiving first-line TKI therapy were subjected to rebiopsies of tumor tissue to determine the presence of T790M mutation. However, rebiopsy is not always feasible for many of the patients.[4]

One alternative method that could be employed for the detection of T790M is the circulating tumor deoxyribonucleic acid (ctDNA) test. The ctDNA genotyping is a specific and sensitive biomarker test that can be used for the detection of EGFR mutation. The ctDNA can be extracted from plasma and used for tumor-specific molecular marker detection. Compared to conventional rebiopsy of tumor tissue in patients who have progressed, ctDNA possesses several advantages such as less invasive, faster, lower costs, and having minimal risk of complications for patients. The concordance between plasma ctDNA test and tumor rebiopsy result in NSCLC patients in Asia Pacific was found to be 78%, with a sensitivity of 50% and specificity of 97%.[3] T790M was detected in 47% of NSCLC patients with acquired EGFR-TKI resistance using the plasma ctDNA test and can be found either before or after disease progression. Hence, it can be regarded as a poor prognostic factor.[5]

Until now, the T790M mutation in NSCLC patients in Dr. Soetomo General Hospital, Surabaya, Indonesia, had never been reported. The aim of this study is to determine the prevalence of T790M and other EGFR mutations in lung adenocarcinoma patients who progressed after the first-line EGFR-TKI using ctDNA test.

MATERIALS AND METHODS

This was a retrospective cohort study based on the medical records of lung adenocarcinoma patients in the Oncology Outpatient Clinic of Dr. Soetomo General Hospital, Surabaya, Indonesia, a tertiary referral hospital in Indonesia, within the period of January 2017 to June 2018. Eligible participants must fulfill the inclusion criteria: those who had been diagnosed with pulmonary adenocarcinoma Stage IV, had positive EGFR mutation, treated and followed-up at the Oncology Outpatient Clinic of Dr. Soetomo General Hospital Surabaya, Indonesia, received first-line EGFR-TKI as treatment, had their disease progressed as evident by radiological (RECIST version 1.1) and/or physician's clinical judgment, and subsequently undergone plasma ctDNA examination. All of the participants characteristic and demographic data, EGFR mutation status, types of first-line EGFR-TKI received, and survival data were recorded. All of the data were obtained from the patient's medical record. Participants with incomplete data or had their plasma ctDNA examination done while on chemotherapy were excluded from the study. This study was approved by the Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (0632/KEPK/Ix/2018).

During the study period, from the first screening, there were a total of 50 patients who had their plasma ctDNA tested and were recorded in the medical records. Eleven patients were excluded due to several reasons, leaving 39 patients who met the inclusion criteria and included in the study as described in Figure 1. We describe our study and the participants filled out the consent form.

Briefly, the procedure for ctDNA test in our hospital was as follows: blood samples were taken from all of the patients and put in ethylenediaminetetraacetic acid tubes. The samples

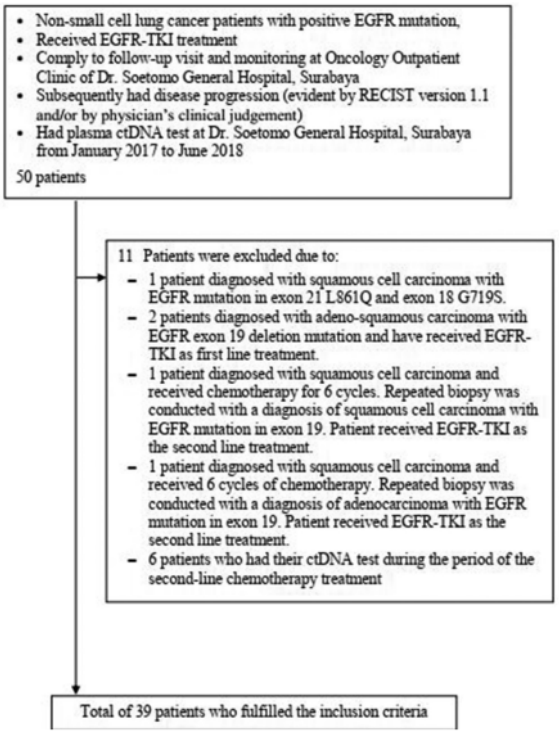

Figure 1: Flowchart of patient recruitment

were then directly sent to a central referral laboratory for further processing within 2 h of blood drawing. Plasma was obtained after a series of centrifugations according to the standard protocol. Fresh plasma were stored at −80°C until further examination. DNA extractions were carried out by using spin column method with QIAamp® circulating nucleic acid kit (QIAGEN, Manchester, UK). Extracted ctDNAs were tested for EGFR mutations using digital detection with the highly sensitive and quantitative Droplet Digital PCR (ddPCR™; Bio-Rad/Molecular MD, Hercules, CA, USA). Assays were performed according to the manufacturer's protocol.

The collected data were assessed using the Shapiro–Wilk test for normality of the distribution. We use the Mann–Whitney U-test or Independent *t*-test to assess the difference between patients who received first-line gefitinib or erlotinib in terms of PFS, with $P < 0.05$ considered as statistically significant. All of the statistical analysis was done using IBM SPSS Statistics Software Version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Subject characteristics

The characteristics of the study participants were summarized in Table 1. The average age of the participant was 57.80 ± 11.29 years (ranged from 35 to 83 years). The majority of them (20 individuals, 51.3%) were in 41–60 years age group. Most of them were female (28 individuals, 71.8%) and nonsmokers (29 individuals, 74.4%). Based on the data of the initial performance score (PS), the majority of the study participants had PS 1 condition (34 individuals, 87.2%).

Most of the histopathology specimens were taken from lung mass (30 samples, 76.9%), mostly by fine-needle aspiration biopsy (FNAB) techniques (in 23 participants, 59.0%). The first-line EGFR-TKI treatment received by the participants was mostly gefitinib (in 33 patients, 84.6%). With respect to EGFR mutation type, EGFR common mutations were a dominant finding (87.2%), consisted of 23 patients with exon 19 deletion mutation (59.0%) and 11 patients with exon 21 L858R mutation (28.2%).

Table 1: Baseline characteristics of the study participants

Characteristics	*n* (%)
Age category (years)	
21-40	3 (7.7)
41-60	20 (51.3)
61-80	15 (38.5)
≥80	1 (2.6)
Sex	
Women	28 (71.8)
Men	11 (28.2)
Smoking history	
Nonsmoker	29 (74.4)
Ex-smoker	4 (10.3)
Smoker	6 (15.4)
Performance status (WHO)	
1	34 (87.2)
2	4 (10.3)
3	1 (2.9)
Histopathological sampling site	
Lung mass	30 (76.9)
Organ metastasis	7 (17.9)
Lung mass and organ metastasis	2 (5.1)
Histopathological sampling method	
Fine-needle aspiration	23 (59.0)
Bronchoscopy	4 (10.3)
Pleural effusion	3 (7.7)
Fine-needle aspiration and bronchoscopy	5 (12.8)
Fine-needle aspiration and pleural effusion	2 (5.1)
Other (open biopsy)	2 (5.1)
EGFR mutation status	
Exon 18 G719S	2 (5.1)
Exon 19 deletion	23 (59.0)
Exon 21 L858R	11 (28.2)
Exon 19 deletion and exon 21 L858R	1 (2.6)
Exon 20 and exon 21 L858R	1 (2.6)
Exon 20, exon 19 deletion and exon 21 L861Q	1 (2.6)
First-line EGFR-TKI treatment	
Gefitinib	33 (84.6)
Erlotinib	6 (15.4)

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitors

Table 2: Result of circulating tumor DNA plasma test

Plasma ctDNA test and its mutation profiles	*n* (%)
Results of plasma ctDNA test	
T790M mutation (+)	18 (46.2%)
T790M mutation (−)	21 (53.8%)
Mutation profile of plasma ctDNA test	
T790M mutation (−)	15 (38.5%)
T790M mutation (−) and exon 19 deletion	5 (12.8%)
T790M mutation (−) and exon 21 L585R	1 (2.6%)
T790M mutation (+)	7 (17.9%)
T790M mutation (+) and exon 19 deletion	7 (17.9%)
T790M mutation (+) and exon 21 L858R	4 (10.3%)

ctDNA: Circulating tumor DNA

T790M mutation status

The result of the T790M mutation status obtained from plasma ctDNA test in this study was illustrated in Table 2. Eighteen out of 39 patients (46.2%) showed positive T790M mutation. Comparing participants with T790M-positive and T790M-negative mutations, there were no significant differences in patient's characteristics in terms of age group, sex, smoking history, and first-line EGFR-TKI treatment received [Table 3].

Progression free survival

In this study, 3 out of 39 participants who fulfill the inclusion criteria had incomplete survival data, so they were not included in the analysis of the PFS. With regard to patients who had disease progression, the median PFS was 9 months and the 12 months survival rate was 36.1% [Table 4]. There was no difference in the median PFS between the two types of EGFR-TKI treatment (gefitinib or erlotinib). The median PFS value for both types of EGFR-TKI treatment was around 9 months ($P = 0.932$) as shown in Table 5.

DISCUSSION

Plasma ctDNA test in lung adenocarcinoma patients who had progressive disease following the first-line EGFR-TKI in Dr. Soetomo General Hospital Surabaya, Indonesia, revealed 46.2% prevalence of positive T790M mutation. This result is encouraging because our study confirmed the conclusions of many other previous studies done in similar circumstances elsewhere.[6-9] It has long been known that EGFR-mutant lung cancer patients who received EGFR-TKI treatment will eventually come to a disease progression due to secondary resistance to EGFR-TKI.[10] Current guidelines recommended tumor tissue rebiopsy to analyze the mechanisms of resistance and identify new targets for further therapy.[11-13] However, it is not easy to obtain tumor samples from patients with EGFR mutation-positive NSCLC that has relapsed after treatment with EGFR-TKIs. The confirmation that plasma ctDNA analysis using digital assay can be used as an alternative and noninvasive method to assess EGFR secondary mutation is a major advance in the management of NSCLC patients. It diverts the necessity of other cumbersome and invasive method which is also vulnerable to false-negative results.

Table 3: Characteristics of T790M-positive and T790M-negative mutant patients

Characteristics	T790M (−)	T790M (+)	*P*
Age category (years), *n* (%)			
21-40	0	3 (16.7)	0.237
41-60	12 (57.1)	8 (44.4)	
61-80	8 (38.1)	7 (38.9)	
≥80	1 (4.8)	0	
Sex, *n* (%)			
Woman	15 (71.4)	13 (72.2)	1.0
Man	6 (28.6)	5 (27.8)	
Smoking history, *n* (%)			
Nonsmoker	16 (76.2)	13 (72.2)	0.792
Ex-smoker	2 (9.5)	2 (11.1)	
Smoker	3 (14.3)	3 (16.7)	
First-line EGFR-TKI treatment, *n* (%)			
Gefitinib	18 (85.7)	15 (83.3)	1.0
Erlotinib	3 (14.3)	3 (16.7)	

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitors

Table 4: Progression-free survival analysis

Analysis of patient's survival	Value
PFS-months	
Median	9
Range	2-48
PFS in 12 months, *n* (%)	
<12	23 (63.9)
≥12	13 (36.1)

PFS: Progression-free survival

Table 5: Median progression-free survival of first-line gefitinib or erlotinib treatment

First-line EGFR-TKI treatment	Median PFS months (range)	*P*
Gefitinib	9 (2-48)	0.932
Erlotinib	9 (3-16)	

PFS: Progression-free survival, TKI: Tyrosine kinase inhibitors, EGFR: Epidermal growth factor receptor

Plasma ctDNA analysis is now approved as a robust and accurate method for the detection of actionable mutations prior treatment selection of first-line TKI, predicting and monitoring response to treatment, and emerging drug resistance mechanisms in NSCLC.[12,14] Many studies had confirmed the high sensitivity and specificity of plasma ctDNA analysis,[8,9] which also showed high overall concordance with tumor tissue samples.[8,15] NSCLC patients from our hospital had previously been involved in a large multicenter IGNITE study conducted in 90 centers from Asia-Pacific and Russia.[3] In that study, plasma ctDNA also had a high concordance with matched tissue/cytology samples (80.5%) albeit with somewhat lower sensitivity (sensitivity 46.9%, specificity 95.6%). EGFR mutation frequencies for evaluable tissue/cytology samples in Asia-Pacific in that study were 49.3% (862/1749).[3]

The prevalence of EGFR mutation in our study is dominated by EGFR common mutation (87.2%) which consisted of exon 19 (59.0%) and exon 21 L858R mutation (28.2%). This result is consistent with other major researches in the field[16-20] which found that the prevalence of EGFR common mutation was around 85%–90%, consisting of exon 19 deletion and exon 21 L858R mutation. Similarly, in the IGNITE study, the proportion of EGFR common mutation was 91.2% in the Asia-Pacific population, which consisted of exon 19 deletion (48.7%) and exon 21 L858R mutation (42.5%).[3] In our study, exon 18 G719S mutation comprised 5.1% of the mutation pool, whereas combination of exon 19 deletion and exon 21 L858R mutation, exon 20 and exon 21 L858R mutation, and triple mutation of exon 19 deletion, exon 20 and exon 21 L861Q mutation were each 2.6% of our study participants, respectively. The result of our study is also consistent with the common findings as summarized by Sharma *et al.*[21] and Pirker *et al.*,[22] where exon 18 mutation was found to be 5% for the total mutation pool and mutation in exon 20 were <1% in proportion. In the IPASS study, several patients were found to possess either EGFR mutation in exon 20, other types of mutation, and/or multiple combinations of mutations.[16] The mutation in exon 20 is associated with primary resistance to EGFR-TKI.[23,24]

The presence of EGFR mutation in NSCLC of adenocarcinoma histology warrants EGFR-TKI as the first-line treatment.[11] With regard to the patient's demographic data, our study results were closely resembled or comparable to the IPASS and WJTOG3405 studies.[16,25] The subject's median age in our study was 58 years (ranged from 35 to 83 years), while in the IPASS study, the median age of the participants was 57 years (range: 24–84 years) and in WJTOG3405 study, it was 64 years (range: 34–74 years). A higher proportion of female patient (71.8%) was found in our study. This result was also similar with NEJ002 and WJTOG3405 studies. In NEJ002 study, the female participants made up 63.2% of the study population,[26] while in WJTOG3405 study, it was 68%.[25] In terms of smoking history, there were more nonsmokers (74.4%) compared to active and ex-smokers. The result of our study is similar to the WJTOG3405

study where nonsmokers were found to be 70.9%.[25] Most participants in our study were in PS 1 condition, which made up 87.2% of the total study population. In comparison, only 64.2% of study participants in IPASS study had PS 1 condition.[16] With regard to the sampling site of histopathological examination for the diagnosis of adenocarcinoma, most specimen samples in our study were obtained from lung mass (76.9%). The most common sampling method for histopathological examination was by FNAB (59%). This finding is consistent with the IGNITE study, where fine-needle aspiration was also identified as the most common method for obtaining samples (51%).[3]

Three types of EGFR-TKI available in Indonesia for first-line treatment of EGFR-mutant NSCLC were gefitinib, erlotinib, and afatinib. Gefitinib was more widely used (84.6%) than erlotinib. This could be due to the fact that gefitinib was the first EGFR-TKI received the approval by National Health Insurance issued by the Indonesian government.[27] Until the end of this study, there were no patients receiving afatinib as the first-line treatment that suffered from disease progression, and therefore, no plasma ctDNA examination done for these patients.

Among patients who had progressed after first-line gefitinib or erlotinib, our study detected 46.2% participants positive for T790M mutation. This result is comparable with the study conducted by Zheng *et al*., which found that the prevalence of T790M-positive mutation patients was 47%.[5] In their study, the combination of T790M-positive mutation with either exon 19 deletion or exon 21 L858R mutation was found to be 29.3%, which is higher compared to single T790M mutation (17.9%).[5] Our result was in contrast to Socinski *et al*.,[13] which found that the prevalence of T790M mutation was 60%, aside from other types of non-EGFR mutations. This difference might be accounted to the difference in race and genetic factors between the Caucasian and Asian population. Further research is needed to confirm this assumption.

In our study, the proportion of patients with negative T790M mutation was 53.8%, in which 38.5% patients had no T790M mutation a[illegible] 15.3% had no T790M mutation but were positive for either exon 19 deletion or exon 21 L858R mutation. This is consistent with Zheng *et al*., where the proportion of patients with negative T790M mutation but were positive for either exon 19 deletion or exon 21 L858R mutation was 6.5%–14.3%.[5] Based on the characteristics of patients, there were no significant differences between T790M positive and T790M negative mutation in terms of age, gender, smoking history, and EGFR-TKI treatment ($P > 0.05$). This is also consistent with the previous study by Zheng *et al*., which had the same findings.[5] Patients with positive T790M mutations from ctDNA test following EGFR-TKI are associated with poor prognosis. It could indicate that tumor cells have exceeded the threshold for tumor growth, and reflect an increase in tumor burden and also metastasis.[5]

PFS in this study was calculated from the time EGFR-TKI treatment was started until the earliest signs of disease progression assessed using RECIST version 1[illegible] and/or clinical worsening. Socinski *et al*. mentioned that resistance to EGFR-TKI will develop in patients after a median PFS of approximately 1-year (average 8–14 months).[13] In the current study, the median PFS was 9 months for both gefitinib and erlotinib. The result of our study is very similar to the WJTOG3405 study which asserted that the median PFS was 9.2 months.[25] Our previous study (thesis, unpublished data) found that the median PFS was 7 months,[27] while the IFUM study reported the median PFS of 9.7 months.[28] Twelve months survival rate in the current study was 36.1%, whereas in our previous study, it was 15.25%.[27] This might be due to immature data in our previous report.

In the current study, there was no difference in median PFS between the two types of EGFR-TKI treatment (gefitinib or erlotinib). The median PFS of gefitinib and erlotinib were 9 months, respectively ($P = 0.932$). In WJOG5108 L study comparing gefitinib and erlotinib, it was found that the median PFS for gefitinib was 8.3 months, while the median PFS for erlotinib was 10 months.[29]

There are several mechanisms of resistance to EGFR-TKI which result in disease progression. The T790M mutations are presumed to cause resistance to EGFR TKI through a variety of mechanisms. One of which is by steric hindrance, which results in the decrease of reversible TKI binding, increased bound affinity with ATP, and increased phosphorylation levels, which ultimately result in the decrease of EGFR-TKI potential.[13] Other review suggests that the mutation causes changes in the tridimensional tyrosine kinase domain structure and prevents gefitinib or erlotinib from binding to EGFR.[30]

CONCLUSIONS

In EGFR-mutated lung adenocarcinoma patients who had disease progression after the first-line EGFR-TKI, plasma ctDNA examination is a valid alternative method for tumor rebiopsy. Our study confirmed the conclusions of many other previous studies done in the same circumstances elsewhere. Using plasma ctDNA test in Dr. Soetomo General Hospital Surabaya, Indonesia, the proportion of T790M mutation in such patients was 46.2%. There were no significant differences between T790M-positive and T790M-negative mutations in terms of the age, sex, smoking history, and the type of EGFR-TKI used. Prior to the first-line EGFR-TKI treatment, EGFR common mutation in exon 19 and exon 21 was detected in 87.2% of the patients. The median PFS of patients receiving gefitinib or erlotinib as the first-line treatment was 9 months.

Acknowledgment

All authors would like to thank Ms. Roselini Ngiono B.Sc for manuscript proofread and her recommendations to

improve our manuscript. The plasma ctDNA test was supported by AstraZeneca Ltd, Indonesia but it does not interferred in manuscript design and preparation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: Epidemiology, etiology, and prevention. Clin Chest Med 2011;32:605-44.
2. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, *et al*. Non-small cell lung cancer, version 6.2015. J Natl Compr Canc Netw 2015;13:515-24.
3. Han B, Tjulandin S, Hagiwara K, Normanno N, Wulandari L, Laktionov K, *et al*. EGFR mutation prevalence in Asia-Pacific and Russian patients with advanced NSCLC of adenocarcinoma and non-adenocarcinoma histology: The IGNITE study. Lung Cancer 2017;113:37-44.
4. Jenkins S, Yang JC, Ramalingam SS, Yu K, Patel S, Weston S, *et al*. Plasma ctDNA analysis for detection of the EGFR T790M mutation in patients with advanced non-small cell lung cancer. J Thorac Oncol 2017;12:1061-70.
5. Zheng D, Ye X, Zhang MZ, Sun Y, Wang JY, Ni J, *et al*. Plasma EGFR T790M ctDNA status is associated with clinical outcome in advanced NSCLC patients with acquired EGFR-TKI resistance. Sci Rep 2016;6:20913.
6. Wang Z, Cheng Y, An T, Gao H, Wang K, Zhou Q, *et al*. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): A phase 2, single-arm, multicentre clinical trial. Lancet Respir Med 2018;6:681-90.
7. Seki Y, Fujiwara Y, Kohno T, Yoshida K, Goto Y, Horinouchi H, *et al*. Circulating cell-free plasma tumour DNA shows a higher incidence of EGFR mutations in patients with extrathoracic disease progression. ESMO Open 2018;3:e000292.
8. Ishii H, Azuma K, Sakai K, Kawahara A, Yamada K, Tokito T, *et al*. Digital PCR analysis of plasma cell-free DNA for non-invasive detection of drug resistance mechanisms in EGFR mutant NSCLC: Correlation with paired tumor samples. Oncotarget 2015;6:30850-8.
9. He C, Zheng L, Xu Y, Liu M, Li Y, Xu J. Highly sensitive and noninvasive detection of epidermal growth factor receptor T790M mutation in non-small cell lung cancer. Clin Chim Acta 2013;425:119-24.
10. Metro G, Crinò L. Advances on EGFR mutation for lung cancer. Transl Lung Cancer Res 2012;1:5-13.
11. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines). National Comprehensive Cancer Network Inc.; 2018.
12. Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, *et al*. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: Guideline from the College of American Pathologists, the International Association for the study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med 2018;142:321-46.
13. Socinski MA, Villaruz LC, Ross J. Understanding mechanisms of resistance in the epithelial growth factor receptor in non-small cell lung cancer and the role of biopsy at progression. Oncologist 2017;22:3-11.
14. Herbreteau G, Vallée A, Charpentier S, Normanno N, Hofman P, Denis MG. Circulating free tumor DNA in non-small cell lung cancer (NSCLC): Clinical application and future perspectives. J Thorac Dis 2019;11:S113-26.
15. Lee JY, Qing X, Xiumin W, Yali B, Chi S, Bak SH, *et al*. Longitudinal monitoring of EGFR mutations in plasma predicts outcomes of NSCLC patients treated with EGFR TKIs: Korean lung cancer consortium (KLCC-12-02). Oncotarget 2016;7:6984-93.
16. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
17. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
18. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
19. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-lung 6): An open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
20. Berois N, Touya D, Ubillos L, Bertoni B, Osinaga E, Varangot M. Prevalence of EGFR mutations in lung cancer in Uruguayan population. J Cancer Epidemiol 2017;2017:Article ID 6170290. https://doi.org/10.1155/2017/6170290.
21. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169-81.
22. Pirker R, Herth FJ, Kerr KM, Filipits M, Taron M, Gandara D, *et al*. Consensus for EGFR mutation testing in non-small cell lung cancer: Results from a European workshop. J Thorac Oncol 2010;5:1706-13.
23. Wu JY, Wu SG, Yang CH, Gow CH, Chang YL, Yu CJ, *et al*. Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response. Clin Cancer Res 2008;14:4877-82.
24. Noronha V, Choughule A, Patil VM, Joshi A, Kumar R, Susan Joy Philip D, *et al*. Epidermal growth factor receptor exon 20 mutation in lung cancer: Types, incidence, clinical features and impact on treatment. Onco Targets Ther 2017;10:2903-8.
25. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, *et al*. 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;11:121-8.
26. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, *et al*. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2013;24:54-9.
27. Fatmawati F. The profile of non-small cell lung cancer patients who received tyrosine-kinase inhibitors as first-line therapy in Dr. Soetomo General Academic Hospital, Surabaya. Indonesian language. [Thesis]. Surabaya: Universitas Airlangga, 2016. Available form http://repository.unair.ac.id/id/eprint/39681.
28. Douillard JY, Ostoros G, Cobo M, Ciuleanu T, McCormack R, Webster A, *et al*. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: A phase-IV, open-label, single-arm study. Br J Cancer 2014;110:55-62.
29. Urata Y, Katakami N, Morita S, Kaji R, Yoshioka H, Seto T, *et al*. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. J Clin Oncol 2016;34:3248-57.
30. Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Rev 2014;23:356-66.

T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

ORIGINALITY REPORT

16%	15%	13%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Laksmi Wulandari, Gatot Soegiarto, Anna Febriani, Farah Fatmawati, Sahrun. "Comparison of Detection of Epidermal Growth Factor Receptor (EFGR) Gene Mutation in Peripheral Blood Plasma (Liquid Biopsy) with Cytological Specimens in Lung Adenocarcinoma Patients", Indian Journal of Surgical Oncology, 2020 Publication	1%
2	theoncologist.alphamedpress.org Internet Source	1%
3	ysmu.am Internet Source	1%
4	www.sap.org.ar Internet Source	1%
5	dspace.ankara.edu.tr Internet Source	1%
6	www.jthoracdis.com Internet Source	

		1 %
7	cancercommun.biomedcentral.com Internet Source	1 %
8	"Genomic Applications in Pathology", Springer Science and Business Media LLC, 2019 Publication	1 %
9	Sun Min Lim, San-Duk Yang, Sangbin Lim, Seong Gu Heo et al. "Molecular landscape of osimertinib resistance in patients and patient-derived preclinical models", Therapeutic Advances in Medical Oncology Internet Source	1 %
10	docksci.com Internet Source	1 %
11	linknovate.com Internet Source	1 %
12	discovery.researcher.life Internet Source	1 %
13	www.apsresp.org Internet Source	1 %
14	slidelegend.com Internet Source	<1 %
15	www.scribd.com Internet Source	<1 %

16	www.clinicaltrials.gov Internet Source	<1 %
17	s3-us-west-1.amazonaws.com Internet Source	<1 %
18	synapse.koreamed.org Internet Source	<1 %
19	urologyannals.com Internet Source	<1 %
20	ecommons.aku.edu Internet Source	<1 %
21	Mark A. Socinski, Liza C. Villaruz, Jeffrey Ross. "Understanding Mechanisms of Resistance in the Epithelial Growth Factor Receptor in Non‐Small Cell Lung Cancer and the Role of Biopsy at Progression", The Oncologist, 2017 Publication	<1 %
22	nrs.harvard.edu Internet Source	<1 %
23	www.spandidos-publications.com Internet Source	<1 %
24	f1000research.com Internet Source	<1 %
25	jtd.amegroups.com Internet Source	<1 %

26	Yusuke Okuma, Mototsugu Shimokawa, Kana Hashimoto, Hideaki Mizutani et al. " Uncommon mutations conducted with osimertinib in patients with NSCLC: a study protocol of phase 2 study (UNICORN/TCOG1901) ", Future Oncology, 2022 Publication	<1 %
27	cyberleninka.org Internet Source	<1 %
28	ecancer.org Internet Source	<1 %
29	respiratory-research.biomedcentral.com Internet Source	<1 %
30	www.frontiersin.org Internet Source	<1 %

Exclude quotes	Off	Exclude matches	< 10 words
Exclude bibliography	On		

T790M mutations identified by circulating tumor DNA test in lung adenocarcinoma patients who progressed on first-line epidermal growth factor receptor-tyrosine kinase inhibitors

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6