MINISTRY OF EDUCATION AND TRAINING

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VINUNIVERSITY

THE EFFICACY OF AFATINIB AND GEFITINIB AS FIRST-LINE THERAPY IN ADVANCED-STAGE NON-SMALL CELL LUNG CANCER (NSCLC) WITH EGFR MUTATION-POSITIVE IN VIETNAMESE PATIENTS

By

NGUYEN DINH TUNG

THESIS

PRESENTED TO COLLEGE OF HEALTH SCIENCES

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IN CANDIDACY OF GRADUATE MEDICAL EDUCATION

IN INTERNAL MEDICINE

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THESIS/DISSERTATION COMMITTEE APPROVAL PAGE

The thesis/dissertation entitled **"The efficacy of afatinib and gefitinib as first-line therapy in advanced-stage non-small cell lung cancer (NSCLC) with EGFR mutation-positive in Vietnamese patients"** by Nguyen Dinh Tung, supervised by Pham Van Luan, M.D, PhD, was successfully defended/approved on 28th February 2024. All revisions suggested by the thesis/dissertation Committee have been addressed, and the thesis/dissertation has been endorsed by the Committee.

Student's Name:	Nguyen Dinh Tung
Degree:	Residency
Title:	Resident Doctor
Examining Committee:	Chair: Assoc. Prof. Le Cu Linh, MD., PhD

Le Cu Linh
Chair:
Assoc. Prof., MD., PhD

Pham Van Luan
Direct Supervisor
MD., PhD

Le Van Phuoc
Secretary
Prof., MD., MPH

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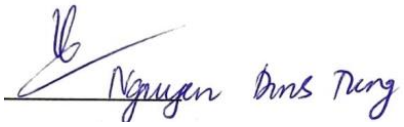
Hanoi, December 20th, 2023



DECLARATION

I hereby declare that this thesis entitled “The efficacy of Afatinib and Gefitinib as first-line therapy in advanced-stage non-small cell lung cancer (NSCLC) with EGFR mutation-positive in Vietnamese patients” is my own work, all information in the thesis is accurate and truthful, with full citations of the references, and does not violate the laws regarding intellectual property.

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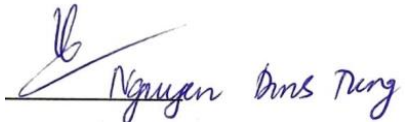

ABBREVIATIONS LIST

No.	Abbreviation	Full Form
1	ACTH	Adrenocorticotropic hormone
2	AJCC	American Joint Committee on Cancer
3	ALK	Anaplastic lymphoma kinase
4	ALT	Alanine transaminase
5	AST	Aspartate transaminase
6	CBC	Complete blood count
7	CI	Confidence interval
8	CT	Computed tomography
9	DRC	Disease control rate
10	ECOG	Eastern Cooperative Oncology Group
11	EGFR	Epidermal growth factor receptor
12	FDA	Food and Drug Administration
13	FDG	Fluorodeoxyglucose
14	FNA	Fine-needle aspiration
15	HR	Hazard ratio
16	LDH	Lactate dehydrogenase
17	MRI	Magnetic resonance imaging
18	NSCLC	Non-small cell lung cancer
19	ORR	Objective response rate
20	OS	Overall survival
21	PD-L1	Programmed death Ligand 1
22	PET	Positron emission tomography
23	PFS	Progression-free survival
24	PS	Performance status
25	ROS1	Rat osteosarcoma
26	SCLC	Small cell lung cancer
27	SIADH	syndrome of inappropriate antidiuretic hormone
28	SUV	Standardized uptake value

29	TKIs	Tyrosine kinase inhibitors
30	TNM	Tumor, Nodes, and Metastasis
31	TROBE	Transparent Reporting of Observational Studies in Epidemiology
32	TTF	Time to treatment failure
33	UICC	Union for International Cancer Control
34	ULN	Upper limit of normal

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ABSTRACT

Background: In Vietnam, Afatinib and Gefitinib are two commonly prescribed TKIs for treating advanced-stage non-small cell lung cancer (NSCLC) patients with EGFR mutation-positive. However, to our knowledge, no comparative studies on the treatment efficacy of these two drugs have been conducted among the patient population in Vietnam.

Objective: This research aims to compare the treatment efficacy of Afatinib and Gefitinib in advanced-stage NSCLC patients with EGFR mutation-positive in Vietnam.

Methods: This is a prospective combined with a retrospective cohort study. The study included 81 advanced-stage NSCLC patients with EGFR mutation-positive, treated with either Afatinib or Gefitinib from January 2019 to September 2022 at the Respiratory Department – Military Central Hospital 108. Patient information was collected from digital medical records to assess primary outcomes, including progression-free survival (PFS), objective response rate (ORR), secondary outcomes such as disease control rate (DCR), and adverse events.

Main findings: This research involved 81 patients with advanced-stage NSCLC with EGFR mutations; 39 received Afatinib (average age 61.9±9.4) and 42 Gefitinib (average age 65.5±11.1). The prevalence of brain metastasis was nearly the same in both groups, 28.2% in the Afatinib group and 26.2% in the Gefitinib group. Median PFS was comparable: median PFS for the Afatinib group was 15.0 ± 2.02 months (95% CI: 11.04 – 18.96), and for the Gefitinib group, it was 15 ± 2.43 months (95% CI: 10.24 – 19.76), with no significant difference (p=0.7). However, ORR was significantly higher in the Afatinib group at 94.9% compared to 76.2% in the Gefitinib group, with a statistically significant p-value of 0.02. DCR was 97.4% in the Afatinib group and 100% in the Gefitinib group, but this difference was not statistically significant (p=0.3). Notably, the incidence of adverse effects was significantly higher in the Afatinib group (82.1%) compared to the Gefitinib group (50%), with a p-value of 0.02. Most adverse events were mild, classified as grade 1 or 2.

Conclusion: In general, the treatment response of afatinib is superior to that of gefitinib. However, adverse events were significantly higher in the Afatinib group but manageable.

Keywords: *non-small-cell lung cancer, EGFR mutation, Afatinib, Gefitinib*

BACKGROUND

Lung cancer is the most common cancer and the leading cause of cancer-related mortality globally. Unfortunately, the majority of lung cancer patients (~80%) are diagnosed at a late stage [1]. Lung cancer is classified histopathologically into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) [2]. Multimodal treatment approaches, including surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and local therapy, are used to treat NSCLC [1, 3]. Despite substantial advancements in early diagnosis and treatment, the overall 5-year survival rate for lung cancer patients is only 19%, regardless of the stage of cancer [1].

In the early 2000s, a better understanding of the molecular pathways that cause malignancy in NSCLC led to the development of treatments that target specific pathways in malignant cells. These agents have been shown to control disease, reduce symptoms, and prolong survival [1, 3]. For NSCLC patients with EGFR mutations, third-generation TKI (Osimertinib), second-generation TKIs (Afatinib, Dacomitinib), and first-generation TKIs (Gefitinib, Erlotinib) are among the preferred first-line targeted treatments [1]. In Vietnam, the use of osimertinib is limited due to its high cost and lack of coverage by health insurance. Therefore, the preferred choices are first- and second-generation TKIs, with afatinib and gefitinib being the most commonly used.

The LUX-Lung 7 trial was the first prospective, worldwide, randomized, head-to-head study to compare afatinib and gefitinib as first-line treatments for EGFR mutation-positive cancer. Although afatinib showed significant improvement in progression-free survival (PFS), time to treatment failure (TTF), and objective response rate (ORR), there was no significant difference in overall survival (OS) observed between afatinib and gefitinib, as updated. It is important to note that the LUX-Lung 7 trial excluded patients with brain metastases and only included participants with an ECOG performance status of 0 or 1 [4]. However, Vietnamese patients diagnosed with advanced-stage NSCLC and EGFR mutations were administered Afatinib and Gefitinib, encompassing individuals with ECOG scores of 2-4 and those affected by brain metastases. In addition, as of December 2023, only four studies conducted in Vietnam on the use of first and second-generation EGFR TKIs for non-small cell lung cancer patients were found on Scopus [5-9].

To address this gap in knowledge, this study aims to compare the efficacy of afatinib and gefitinib in treating advanced-stage non-small cell lung cancer with EGFR mutation-positive in Vietnamese

patients treated in 108 hospital by assessing progression-free survival (PFS), objective response rate (ORR), disease control rate (DRC), and adverse events.

CHAPTER 1. LITERATURE REVIEW

1.1. Epidemiology and risk factors

Lung cancer remains one of the most common and fatal cancers worldwide. In Vietnam, it stands as the second most common cancer and the second leading cause of cancer-related deaths since 2012, resulting in an approximate count of 26 262 incident cases and 23 797 fatalities in 2020 [10].

The primary contributor to lung cancer is cigarette smoking. Individuals who smoke encounter a risk of developing the disease that is ten times higher or more compared to those who do not smoke. According to a large-scale genomic study, one genetic mutation occurs for every fifteen cigarettes smoked [11, 12]. The risk of lung cancer decreases after quitting smoking, with the magnitude of risk reduction increasing with the length of time since cessation. However, even long-term former smokers still maintain a higher risk for lung cancer compared to those who never smoked [13, 14]. Additionally, exposure to environmental tobacco smoke or second-hand smoke is also a known cause of lung cancer, with approximately 20–30% of lung cancer recognized among non-smokers who have been married to smokers for a considerable duration [11].

Other factors that contribute to the risk of lung cancer include exposure to environmental factors like ionizing radiation and various substances (asbestos, bis chloromethyl ether, mustard gas, arsenic, hexavalent chromium, nickel), as well as family history and genetic susceptibility. Additionally, there is evidence linking prior lung conditions such as emphysema, TB, and chronic bronchitis to an elevated risk of developing lung cancer [11, 15].

1.2. Classification of lung cancer

Lung cancers are classified based on pathological diagnosis, following the 2015 guidelines of the World Health Organization. There are four main cell types: small-cell lung cancer (SCLC), squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma. The latter three types are collectively known as non-small cell lung cancer (NSCLC) (Figure 1) [2]. In the United States, the predominant type of lung cancer cases is NSCLC, accounting for 85% of all cases [16]. This proportion is similar in Vietnam, with more than 80% of cases being NSCLC, among which about 70% are adenocarcinoma [9].

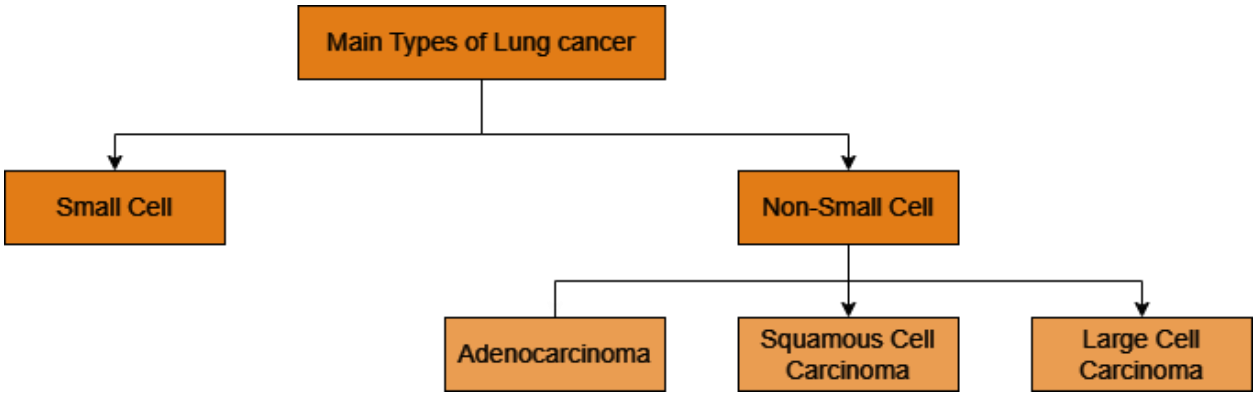


Figure 1.1. Classification of lung cancer with four main cell types.

1.3. Clinical manifestations of lung cancer

In December 2013, the United States Preventive Services Task Force (USPSTF) recommended annual screening for lung cancer using low-dose computed tomography in high risk individuals [17]. Since then, a shift has occurred in how lung cancer typically presents upon diagnosis. Randomized trials demonstrated a significant rise in the count of patients diagnosed at localized stages. Additionally, there was a considerable rise in the proportion of individuals without any lung cancer symptoms and a history of previous malignancy [18, 19].

According to results from a nationwide registry study in 2020 with 9876 patients, the incidence of all examined symptoms rose in accordance with tumor stage. Notably, the absence of symptoms was observed in 59% and 42% of patients diagnosed at stages I and II, respectively. Throughout all stages, cough was the most prevalent symptom, except in stage IV where pain was marginally more frequent. Interestingly, no differences were observed between smokers and non-smokers regarding the presence of symptoms, or in the number of symptoms reported at the time of diagnosis [20].

Overall, the manifestation of lung cancer clinically relies on the type and site of the primary tumor, the extent of local tumor spread, the presence of metastases, or any associated paraneoplastic syndromes [11, 21].

1.3.1. Intrathoracic manifestations

Patients experiencing central or endobronchial growth of the primary lung tumor might manifest symptoms such as cough, hemoptysis, wheezing, stridor, dyspnea, or post obstructive pneumonia. Conversely, peripheral growth of the primary tumor can result in pain due to the involvement of

the pleura or chest wall, restrictive dyspnea, and symptoms resembling a lung abscess caused by tumor cavitation [11].

The regional spread of the tumor within the thorax can lead to a range of complications, including tracheal obstruction, compression of the esophagus, hoarseness resulting from paralysis of the recurrent laryngeal nerve, Horner's syndrome (consisting of enophthalmos, ptosis, miosis, and anhidrosis), and the development of malignant pleural effusions. These symptoms are prevalent in both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), posing a challenge in differentiating between them based solely on symptoms [11].

1.3.2. Extrathoracic metastases manifestations

Metastatic spread outside the thoracic region is common in lung cancer, affecting various organs, with the most common site of metatasis including brain, bones, liver, and adrenal gland. Brain metastases may cause headache, nausea, seizures, or neurological impairments, while bone metastases can cause pain, fractures, or compression of the spinal cord. Liver metastases may manifest as an enlarged liver, pain, weight loss, and fever while adrenal metastases are often asymptomatic [11].

1.3.3. Paraneoplastic phenomena

Paraneoplastic syndromes are a set of organ dysfunction patterns caused by the immune-mediated or secretory function of neoplasms. They are observed in 10–20% of lung cancer patients and may manifest before, during, or after the cancer diagnosis. Small cell carcinoma can lead to the syndrome of inappropriate antidiuretic hormone (SIADH) in 10–15% of patients, while squamous cell carcinoma can cause hypercalcemia in 10% of cases. Other prevalent paraneoplastic syndromes in lung cancer include increased ACTH production, hypercoagulability, anemia, Lambert-Eaton myasthenic syndrome, and peripheral neuropathy. Identifying these syndromes is pivotal as treating the primary tumor can ameliorate or alleviate the symptoms, even if curing the cancer is not feasible [11, 21].

1.4. Diagnosis of non-small-cell lung cancer (NSCLC)

1.4.1. Initial laboratory studies and imaging

Laboratory studies including complete blood count (CBC), liver enzymes, renal function, and bone parameters are mandatory for diagnosis of lung cancer. CBC may detect anemia, neutropenia, or thrombocytopenia. Abnormal liver function test may indicate liver metastasis. Hypercalcemia may

suggest bone metastasis or a paraneoplastic syndrome, whereas an increase in alkaline phosphatase level may signal bone or liver metastasis [22].

Serum LDH is a nonspecific marker for cancer, but elevated LDH level may serve as an unfavorable prognostic indicator in some lung cancer subtypes like small-cell lung cancer and EGFR mutation-positive NSCLC [23].

Chest radiograph offers initial insights into the condition but lacks comprehensive details for characterization and staging. A chest computed tomography (CT) is the cornerstone and is recommended for all patients with either abnormal chest X-ray results or suspected lung cancer [24].

While nearly all lung cancer patients exhibit abnormalities in chest radiography or CT scan, these findings are rarely specific for a precise diagnosis [21]. Nodules or masses with the following features may indicate malignancy: irregular margins, more than 2 cm in size, located in the upper lobe, and abcences of calcifications (Figure 2). Patients may also present with indirect signs of lung malignancy on CT scan: atelectasis, obstructive pneumonia, pleural effusion, or mediastinal widening [25].

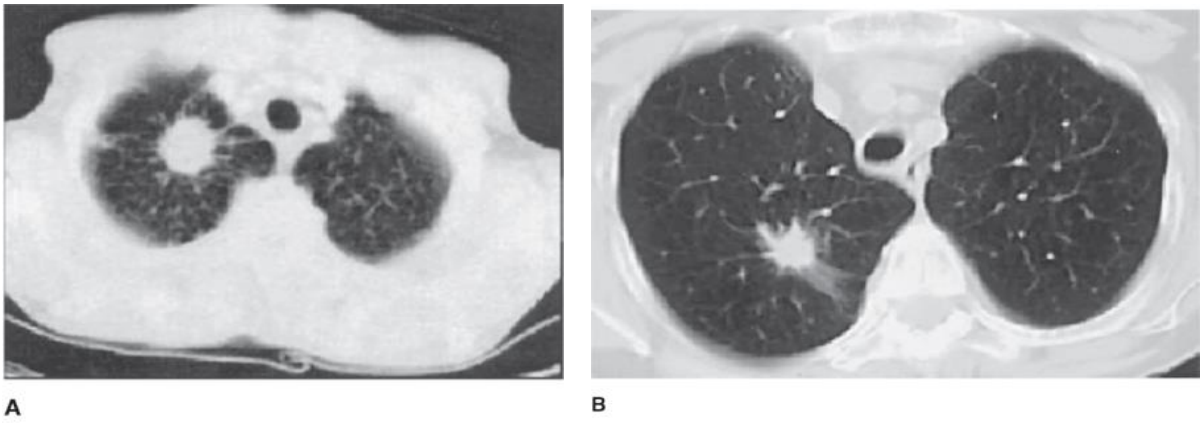


Figure 1.2. CT scan images of solitary pulmonary nodules *[26]*

1.4.2. Confirmation of diagnosis

Tissue samples should be obtained for histopathological analysis to confirm the diagnosis and to indicate the management plan since major initial treatment decisions are determined based on pathological features.

The choice of techniques for obtaining tumor samples depends on various factors such as tumor characteristics (tumor location, size, and type) and technical aspects of the diagnostic procedure (bronchoscopist and pathologist expertise) [11]. Generally, less invasive methods are favored when feasible (Table 1.1).

Table 1.1. Clinical manifestations and suggested sampling methods *[11] [21]*

Clinical manifestations	**Suggested sampling methods**
Central airway lesions	Sputum cytology (*) Bronchoscopic examination
Peripheral airway lesions	Transthoracic biopsy (**)
Malignant pleural effusion	Thoracentesis with an adequate cell block
Suspected metastatic disease	Percutaneous biopsy of a soft tissue mass, lytic bone lesion, bone marrow, pleural or liver lesion
Palpable supraclavicular or cervical lymph nodes	Fine-needle aspiration (FNA)

(*)Sputum cytology is inexpensive, noninvasive and highly specific (nearly 100%) but insensitive and the quality of the specimen may not be adequate for pathological classification and immunohistochemistry testing.

(**) The rate of pneumothorax during CT-guided biopsies of peripheral nodules is significant, ranging from 15% to 30%, particularly in patients with emphysema. [21].

1.4.3. Advanced studies for diagnosis

Following the initial diagnostic, the next step involves identifying potential metastatic locations and evaluating the molecular characteristics of the tumors. Molecular testing, including genetic testing and immunohistochemistry, becomes essential for patients dealing with advanced or metastatic NSCLC since major treatment options are determined based on these factors (Figure 1.3).

1.4.3.1. Imaging for lung cancer staging [11]

Positron emission tomography (PET), CT scan, or ideally, a combined CT-PET, is recommended for all NSCLC patients. To date, PET has primarily been used for staging and identifying metastases in lung cancer and for detecting nodules larger than 15 mm. An SUV (standardized uptake value) exceeding 2.5 on PET indicates a high suspicion of malignancy. However, false negatives may occur in cases involving diabetes, lesions smaller than 8 mm, and slow-growing tumors (like carcinoid tumors or well-differentiated adenocarcinoma). False positives can arise from certain infections and granulomatous diseases (e.g., tuberculosis). Therefore, PET alone should not be relied on for diagnosing lung cancer, mediastinal involvement, or metastases. Combined 18F-FDG PET-CT imaging has shown improved accuracy in staging non-small cell lung cancer compared to either PET or CT (Figure 1.3).

For detecting brain metastases, magnetic resonance imaging (MRI) is the most effective method. While MRI can occasionally be beneficial in specific scenarios, such as ruling out brachial plexus involvement in superior sulcus tumors, its role in NSCLC staging is generally limited.

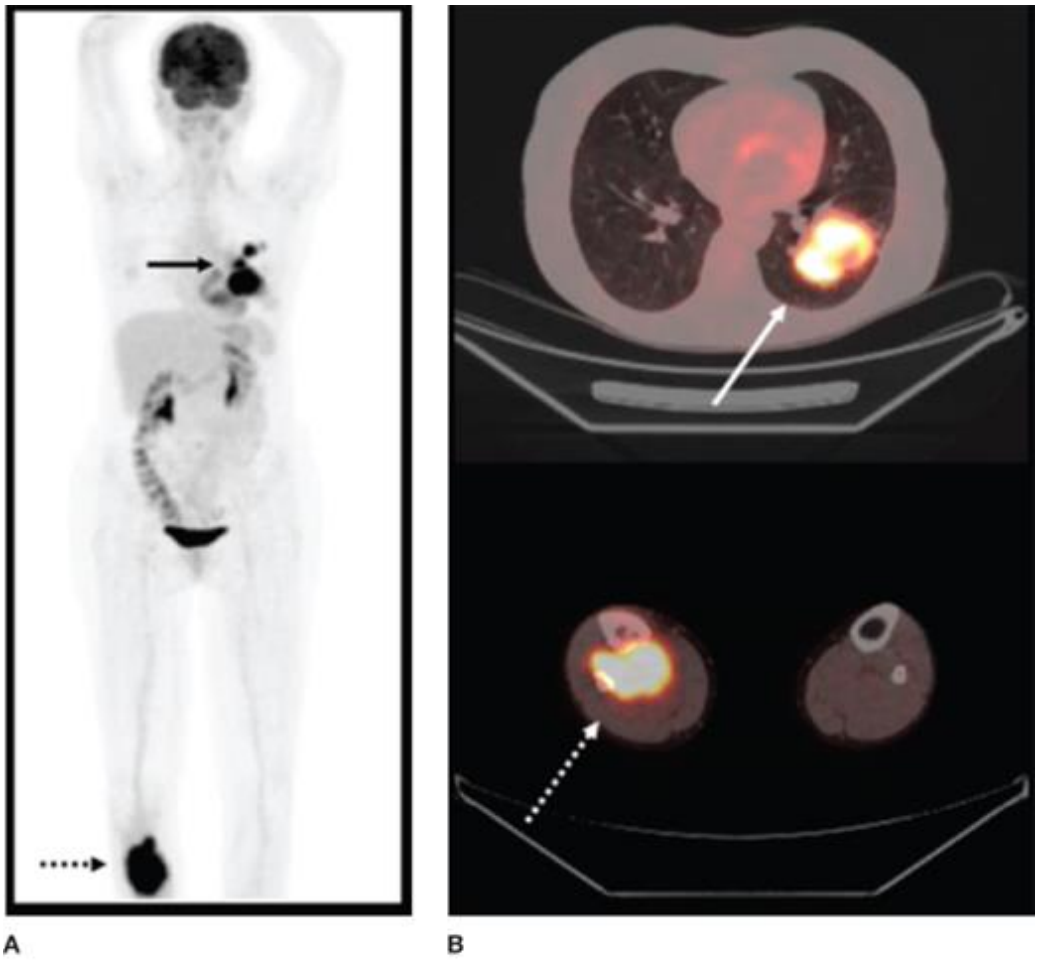


Figure 1.3. Whole-body coronal PET (A) and fused transaxial PET/CT (B) reveal elevated FDG uptake in the lung tumor and unexpected focal FDG uptake in the left proximal tibia *[27].*

1.4.3.2. Molecular diagnostics [11, 28, 29]

From 2006 to 2013, there was a rapid decline in mortality in subtype NSCLC of lung cancer. This decline began to accelerate in 2013, explained particularly by the approvals and utilization of targeted therapies and the recommendations of routine testing for molecular alterations in NSCLC patients. To date, testing for genetic mutations has become the standard approach for the treatment of advanced NSCLC [29]. This includes testing for mutations in EGFR and in BRAF V600E, searching for translocations in the genes encoding ALK (anaplastic lymphoma kinase) and ROS1 (rat osteosarcoma), and more recently, evaluating the expression of PD-L1 (programmed death

ligand 1). Notably, most of these molecular tests can now be conducted using small biopsy samples or cytologic specimens [11, 28].

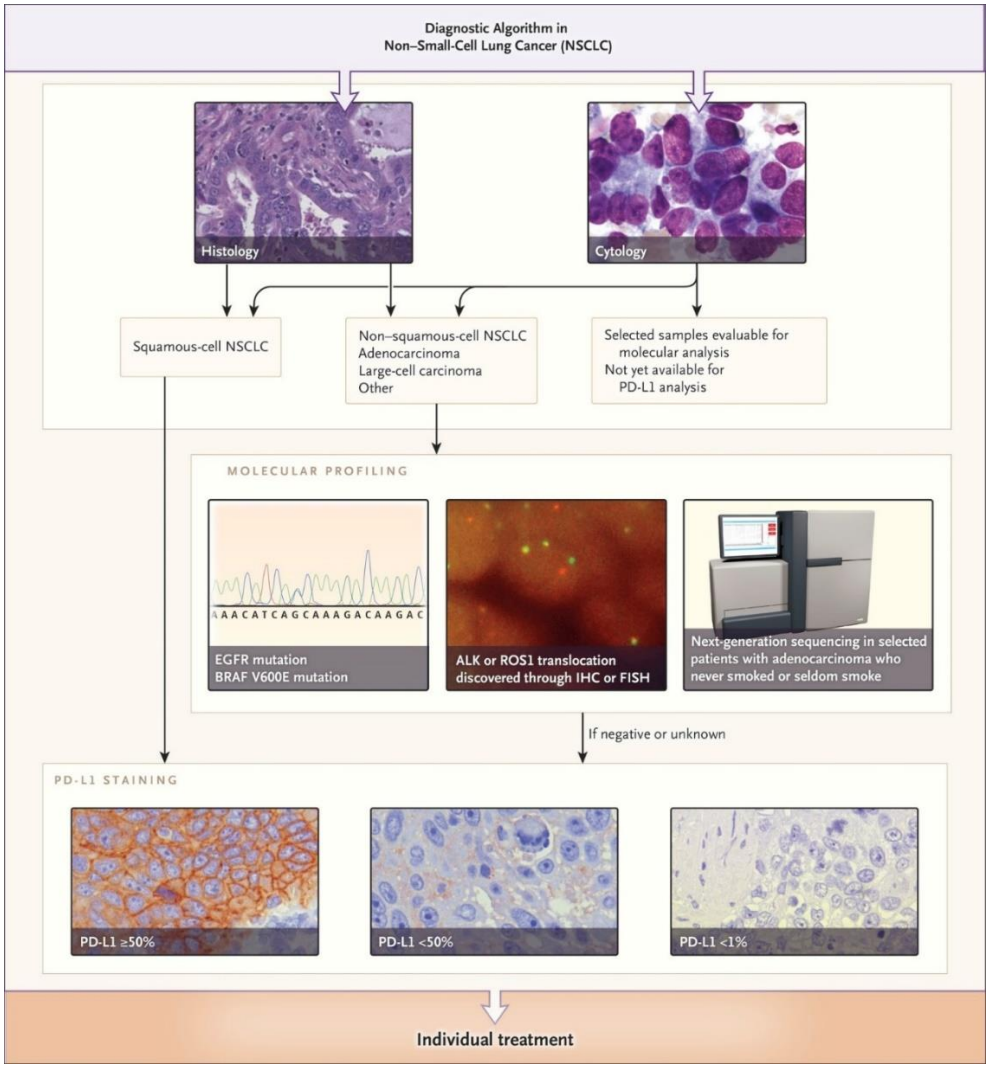


***Figure 1.4. Diagnosis Algorithm For NSCLC** [28]*

1.5. Staging of Non-small cell lung cancer

Staging NSCLC is crucial for assessing disease extent and guiding treatments. The TNM system, representing Tumor, Nodes, and Metastasis, is commonly employed for NSCLC staging. Tables 1.2 and table 1.3 present the 8th edition of TNM classification and stage grouping for lung cancer, published by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) [30].

Table 1.2. Clinical classification UICC TNM 8

Primary tumor (T)

Tx	Primary tumour cannot be assessed, or tumour proved by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy.
T0	There is no evidence of a primary tumour
Tis	Carcinoma *in situ*
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma
T1a	Tumour 1 cm or less in greatest dimension
T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension
T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features: - Involves the main bronchus regardless of the distance to the carina, but without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of or the entire lung
T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura, chest wall (including superior sulcus tumours) phrenic nerve, parietal pericardium;

	or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour more than 7 cm or of any size that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis in a single organ
M1c	Multiple extrathoracic metastasis in a single or multiple organs

Table 1.3. Staging and stage grouping UICC TNM 8

Stage	T	N	M
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi T1a	N0 N0	M0 M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c; T2a,b T3	N1 N0	M0
Stage IIIA	T1a-c; T2a,b T3 T4	N2 N1 N0, N1	M0
Stage IIIB	T1a-c; T2a,b T3, T4	N3 N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

1.6. Treatment of advanced non-small cell lung cancer

Advanced NSCLC refers to lung cancer with metastases or recur following initial definitive treatment. Those patients are generally treated with systemic therapy including chemotherapy, antiangiogenic therapy, targeted therapy, or immunotherapy. However, the selection of treatment strategies needs to consider many factors: histopathology, age, performance status, comorbidities, and the patient's preferences. The ideal approach is to have treatment decisions deliberated by a multidisciplinary tumor board (MTB), which can suggest additional investigations and modify the treatment modalities [31].

1.6.1. Treatment of advanced NSCL with driver mutation absent or unknown

Platinum-based chemotherapy remains the standard of care for advanced NSCLC without actionable mutations [1, 32]. Nonetheless, in cases where patients exhibit tumor PD-L1 expression of 50% or higher, pembrolizumab monotherapy stands as the favored initial treatment for nonsquamous or squamous NSCLC (Figure 1.5) [32]. In KEYNOTE-024 Trial, pembrolizumab monotherapy has shown a notable improvement in both PFS and OS compared to platinum-based chemotherapy as first-line therapy in advanced NSCLC patients with a high level of tumor PD-L1 expression (50%) [33].

For advanced NSCLC patients with regardless of PD-L1 status, immunotherapy in combination with chemotherapy is considered standard approach which was suggested by many trials: KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, KEYNOTE-407, IMpower110, IMpower130, IMpower150, CheckMate 227, CheckMate 9LA, and MYSTIC [32]. However, there is no single chemotherapy combination that is considered the optimal therapy selection.

Figure 1.5 illustrates the treatment options available for advanced non-small cell lung cancer (NSCL) in cases where driver mutations are absent.

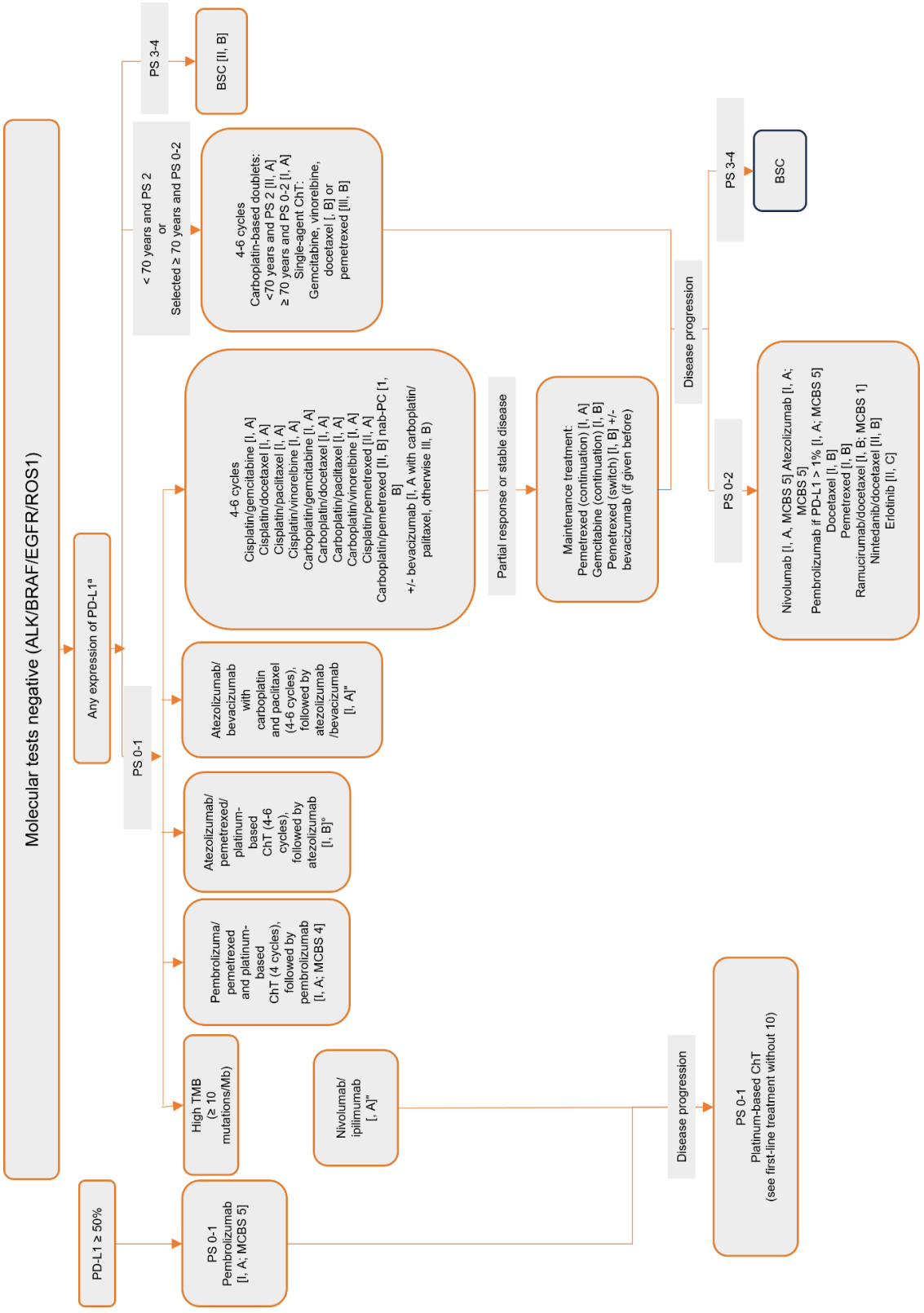


***Figure 1.5. Treatment options for patients with molecular test negative** [32]*

1.6.2. Treatment of advanced NSCL with driver mutation present

In advanced NSCLC, targeted therapy is a crucial treatment. When oncogenic driver mutations are present, targeted therapy offers patients the opportunity to use oral therapy that displays significant antitumor activity and improved survival outcomes compared to traditional chemotherapy. Therefore, it is recommended that appropriate testing for oncogenic mutations be included in the routine diagnostic assessment of advanced NSCLC patients [1, 32]. Various genetic alterations including mutation, fusion, and deletion have been reported in multiple genes such as EGFR, ALK, ROS1, RET, MET, …

1.6.2.1. EGFR mutations

The identification of actionable mutations in EGFR has been the primary step in the progress of targeted therapy for NSCLC [34]. Among these mutations, the exon 19 deletions and exon 21 L858R point mutations are the most prevalent [35]. While they are present in 10 to 20% of white NSCLC patients, they have a higher frequency in East Asian patients (approximately 48%). These mutations are often linked with minimal smoking history or nonsmoking history, younger age, and adenocarcinoma histology [36]. Tumors carrying these mutations demonstrate high sensitivity to small-molecule EGFR tyrosine kinase inhibitors (TKIs). According to a meta-analysis of randomized trials involving 1649 patients comparing EGFR TKIs with chemotherapy, EGFR TKIs showed significant extended PFS in overall and in all subgroups (median PFS, 9.6 to 13.1 months compared to 4.6 to 6.9 months; HR for progression or death, 0.37; 95% CI, 0.32 to 0.41; $P<0.001$). In addition, tumors with exon 19 deletions exhibited a 50% greater benefit from EGFR TKIs than those with exon 21 L858R substitution. Never-smokers and women also showed greater benefits from this targeted therapy compared to current or former smokers and men, respectively [37].

Currently, the FDA has approved several oral small-molecule EGFR TKIs including erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib [1].

1.6.2.2. ALK and ROS1 translocations

Translocations of ALK are observed in 2 to 7% of NSCLC patients, while ROS1 translocations are found in 1 to 2% of patients. These translocations result in new fusion genes that have transforming activity. Like EGFR, ALK and ROS1 rearrangements are commonly related to younger age, history of light smoking or nonsmoking, as well as adenocarcinoma histology [38, 39].

In patients with lung tumors harboring ALK rearrangements, crizotinib stands as a first-generation ALK TKI, whereas brigatinib, alectinib, and ceritinib are second-generation ALK TKIs approved as first-line treatment. Regarding patients with ROS1 translocation, crizotinib has shown clinical effectiveness with a 72% response rate and a median progression-free survival of 19.2 months. There is ongoing evaluation for additional agents [32, 40].

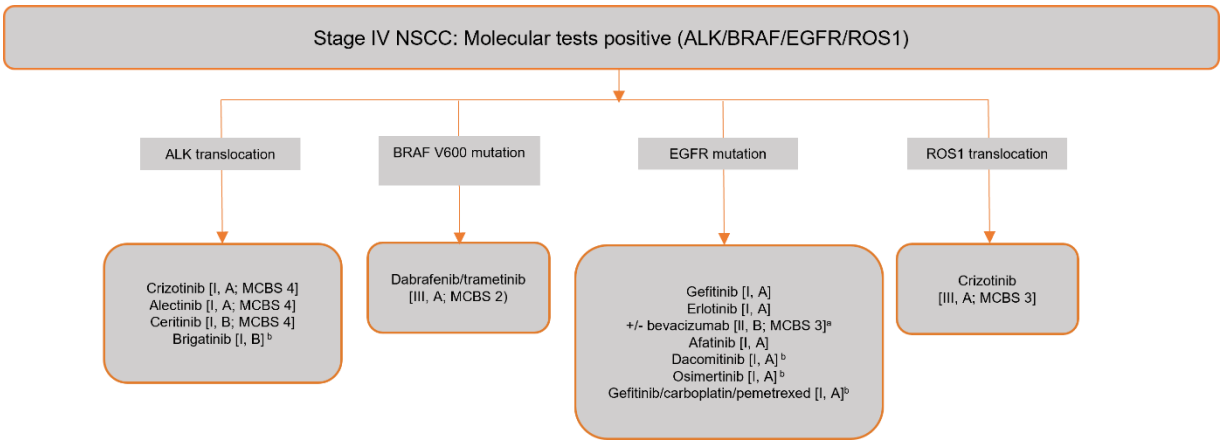


Figure 1.6. Treatment options for patients with molecular tests positive

1.6.2.3. Other targetable alterations

Less common driver mutations have been detected in patients with NSCLC, including BRAF, RET, TRK, MET, and KRAS. Specific inhibitors are available for most of these mutations, and they should be integrated into the overall sequence of treatments for a given patient [41].

1.7. Afatinib and Gefitinib in advanced NSCLC with EGFR mutation -positive

1.7.1. Gefitinib

Gefitinib is recommended as initial therapy for patients with metastatic NSCLC carrying EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It works by specifically attaching to the tyrosine kinase domain, impeding ATP binding and subsequent receptor autophosphorylation, ultimately inhibiting signal transduction [42]. Gefitinib was the first FDA-approved EGFR TKI for NSCLC, with its initial clinical trials commencing in the early 2000s. The Iressa Pan-Asia Study (IPASS) was a phase III, randomized, open-label trial that compared the use of gefitinib to carboplatin-paclitaxel in East Asian patients with advanced NSCLC and nonsmoking or former light smoking. This is a pivotal trial that demonstrated, for the first time, the superiority of targeted therapy (gefitinib) over chemotherapy (carboplatin-paclitaxel) in a specific patient population [43,

44]. The study randomly assigned 609 patients to receive gefitinib and 608 patients to receive carboplatin-paclitaxel, the primary endpoint was PFS. The result showed that gefitinib was superior to carboplatin-paclitaxel in terms of PFS in the intention-to-treat population and also showed its noninferiority. The 12-month rates of PFS were 24.9% for gefitinib and 6.7% for carboplatin-paclitaxel [45]. Following IPASS study, several trials have recruited patients based on EGFR mutation status, comparing treatment EGFR TKI versus platinum-based chemotherapy. Like IPASS, all subsequent trials have shown that EGFR TKIs result in longer progression-free survival (PFS) compared to platinum-based chemotherapy. However, none of these trials have shown a survival advantage due to cross-over effects (Table 1.4) [44].

Table 1.4. Trials that compare the treatment of EGFR TKIs versus platinum-based chemotherapy.

Study	Treatment	N	Median PFS (months)	Median OS (months)
Maemondo	Gefitinib versus carboplatin/paclitaxel	230	10.8 versus 5.4 (p 0.001)	30.5 versus 23.6 (p 0.31)
Mitsudomi	Gefitinib versus cisplatin/docetaxel	177	9.2 versus 6.3 (p 0.0001)	36 versus 39 HR 1.19
OPTIMAL	Erlotinib versus carboplatin/gemcitabine	165	13.1 versus 4.6 (p 0.0001)	HR 1.065 (p 0.65)
EURTAC	Erlotinib versus platinum-based chemotherapy	174	9.7 versus 5.2 (p 0.0001)	19.3 versus 19.5 (p 0.87)
LUX-Lung 3	Afatinib versus CDDP/Pemetrexed	345	11.1 versus 6.9 (p 0.0004)	Not reported
LUX-Lung 6	Afatanib versus gemcitabine/CDDP	364	11.0 versus 5.6 (p 0.0001)	HR 0.95 (p 0.76)

In 2018, Esther HA Sim et al. conducted a systemic review of Gefitinib's efficacy in the treatment of advanced NSCLC. The review included 35 randomized controlled trials (RCTs) involving 12,089 patients [46]. The study revealed that patients with EGFR mutation-positive status exhibited better progression-free survival when treated with gefitinib compared to both first-line and second-line chemotherapy (HR 0.47, 95% CI 0.36 to 0.61, P < 0.00001; HR 0.24, 95% CI 0.12 to 0.47, P < 0.0001, respectively). When utilized as a maintenance therapy post-chemotherapy, gefitinib demonstrated an improvement in both overall and progression-free survival (HR 0.39, 95% CI 0.15 to 0.98, P = 0.05; HR 0.17, 95% CI 0.07 to 0.41, P < 0.0001, respectively) in a phase III study when compared against a placebo. Gefitinib also showed a more favorable safety profile compared to existing chemotherapy regimens. Adverse effects related to gefitinib comprised skin rash, diarrhea, and liver enzyme abnormalities, while chemotherapy resulted in side effects like neutropenia, anemia, and neurotoxicity. Regarding quality of life, gefitinib displayed enhancements in various measures such as FACT-L (Functional Assessment of Cancer Therapy-Lung), lung cancer subscale, and Trial Outcome Index scores in comparison to chemotherapy [46].

1.7.2. Afatinib

Afatinib, classified as a second-gen EGFR TKI, was developed to address resistance caused by the T790M mutation to first-gen EGFR TKIs. These second-gen EGFR TKIs are small compounds that form a covalent connection with the intracellular kinase domain of the EGFR protein. Apart from binding irreversibly to wild-type EGFR, HER2, and HER4, these agents also bind to EGFR that harbors the T790M mutation [47]. LUX-Lung 3, a phase 3 trial, investigated afatinib versus a cisplatin and pemetrexed combination in metastatic NSCLC patients with EGFR mutations positive. This study revealed that the afatinib group displayed a notably longer median PFS compared to the group treated with cisplatin plus pemetrexed (11.1 months versus 6.9 months; hazard ratio [HR] of 0.58; p = 0.001). Based on these findings, afatinib has gained approval for treating NSCLC patients with EGFR mutations as a first-line therapy [48, 49]. The most common side effects associated with afatinib include diarrhea, acne-like dermatitis or skin rash, stomatitis, and hand-foot skin reactions. Additionally, observed adverse events include abnormal liver enzyme, interstitial lung disease, and left ventricular dysfunction [48, 50].

1.7.3. Afatinib and Gefitinib

The LUX-LUNG 7 is the first prospective head-to-head, open-label, randomized phase 2B trial that compared afatinib to gefitinib as the first-line therapy for patients diagnosed with EGFR mutation-positive (specifically del19 or L858R only) NSCLC [4]. This study aimed to assess three primary

endpoints: progression-free survival (PFS), time to treatment failure (TTF), and overall survival (OS). In this trial, 319 patients with stage IIIB/IV EGFR mutation-positive NSCLC were randomly assigned in a 1:1 ratio to either afatinib or gefitinib. As the first-line treatment, afatinib notably reduced the risk of lung cancer progression or death by 27% compared to gefitinib (HR=0.73 [95% CI, 0.57-0.95]; P=0.017). The median PFS for afatinib was 11.0 months (95% CI, 10.6-12.9) versus 10.9 months (95% CI, 9.1-11.5) for gefitinib. Although the study did not reveal a significant disparity in overall survival (OS), there was a tendency toward improved OS with afatinib versus gefitinib (median OS 27.9 months vs. 24.5 months; HR=0.86 [95% CI, 0.66–1.12]; P=0.2580) [4]. This pattern remained consistent in prespecified subgroup analyses based on mutation type (del19, 30.7 vs. 26.4 months; HR, 0.83 [95% CI 0.58–1.17]; P=0.2841) and L858R (25.0 vs. 21.2 months; HR, 0.91 [95% CI 0.62–1.36]; P=0.6585) [51]. In addition, the Afatinib-treated group had a higher rate of adverse events related to a higher degree of tumor necrosis (13% vs. 1%), while Gefitinib-treated patients more frequently experienced increased liver (9% vs. 0%) [4].

Real-world trials conducted in Asian countries have consistently highlighted the efficacy of Afatinib and Gefitinib in NSCLC patients with EGFR mutation- positive [52-54]. A study in Korea involving 467 patients revealed that those treated with Afatinib exhibited a median PFS of 19.1 months, significant longer than patients treated with Gefitinib (13.7 months) [52]. This superior PFS with afatinib was particularly evident in subgroups featuring Del19 or uncommon EGFR mutations [52]. Additionally, a separate study by Su P.L. and colleagues in Taiwan reported that patients receiving afatinib displayed enhanced overall survival (OS) (39.3 vs. 26.0 months; HR 0.65, P = 0.033) and progression-free survival (PFS) (14.1 vs. 11.2 months; HR 0.58, P < 0.001) [53]. These findings collectively underscore the favorable outcomes associated with afatinib compared to gefitinib, emphasizing its efficacy in the treatment of EGFR mutation-positive NSCLC in real-world scenarios across various Asian populations.

Vietnam is a country with a high prevalence of EGFR mutations in advanced NSCLC patients. In a study conducted at the University of Medicine and Pharmacy in Ho Chi Minh City in 2016, involving 332 diagnosed NSCLC patients, the EGFR mutation rate was recorded at 40.7% [55]. Similarly, research conducted by Pham Van Luan (2020), Mai Trong Khoa (2016), and Hoang Anh Vu (2011) also presented consistent findings, reporting rates of 42.6%, 40.1%, and 42%, respectively [56-58]. Given the current conditions in Vietnam, where the majority of EGFR mutation-positive lung cancer patients cannot afford Osimetinib treatment, first and second-generation TKIs remain the preferred medications for this patient group. Also in Vietnam, despite

an estimated 26,262 new cases and 23,797 deaths from lung cancer in 2020, only four studies on the utilization of first and second-generation EGFR TKIs for non-small cell lung cancer patients were discovered on Scopus by December 2023. [5-9]. This research aimed to evaluate the effectiveness of afatinib and gefitinib in treating advanced-stage NSCLC with EGFR mutation-positive in Vietnamese patients.

1.8. Conceptual framework

The following diagram shows the relationship between variables that impact the efficacy of afatinib and gefitinib in the treatment of advanced-stage NSCLC with EGFR mutation-positive in Vietnamese patients.

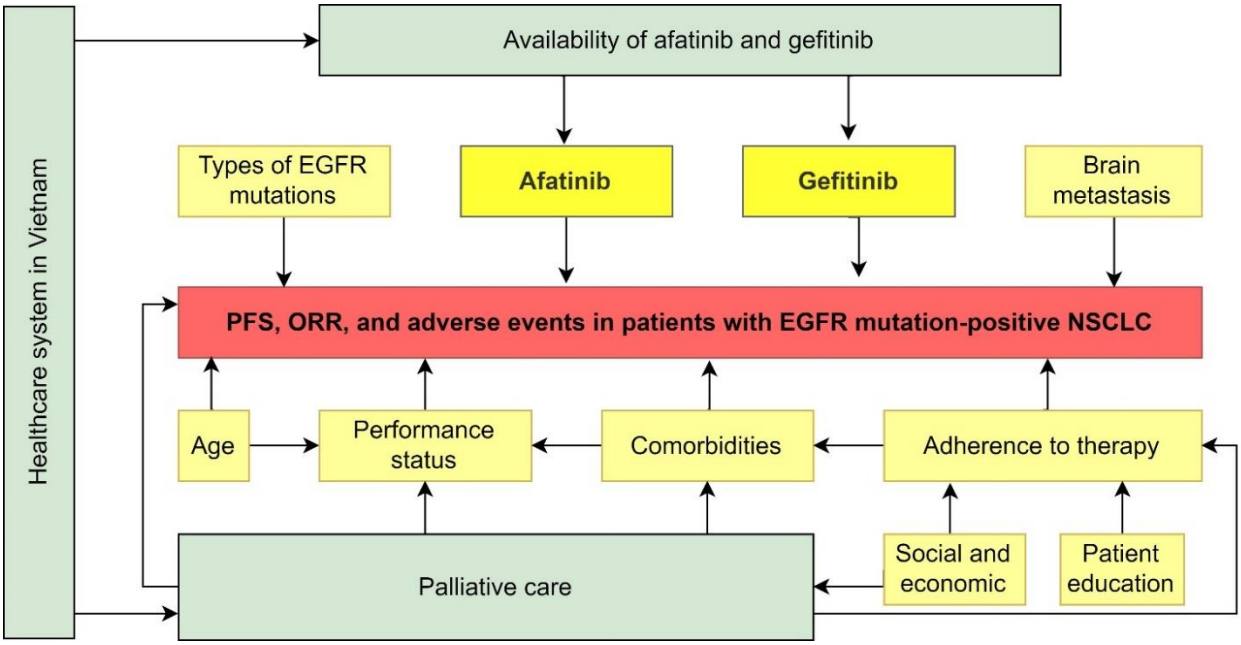


Figure 1.7. Conceptual framework

Therapy outcomes: PFS, ORR	***PFS (Progression-Free Survival)*** is defined as the duration from the initiation of treatment to the date of disease progression or the date of death if the patient passed away earlier. ***ORR (Objective Response Rate)*** refers to the proportion of patients within the study exhibiting a partial or complete response to the treatment within a specified period.
Immediate determinants outcome: performance status, types of EGFR mutations, brain metastasis, age, comorbidities, adherence	***Performance status (PS):*** a score that estimates patient's ability to perform certain activities of daily living without assistance. In this study, we use ECOG PS scale, with:

to therapy, and early palliative care	PS 0: fully active. PS 1: restricted in strenuous activity. PS 2: restricted in work activity but ambulatory and capable of self-care. PS 3: capable of limited self-care. PS 4: completely disabled. PS 5: dead. ***Types of EGFR mutations*** and ***present of brain metastasis*** can impact patient's prognosis. ***Advanced age*** and ***comorbidities*** can lower a patient's PS score and survival prognosis, which in turn affects progression-free survival (PFS), and objective response rate (ORR). ***Adherence to therapy*** is crucial for controlling underlying conditions and improving outcomes. This factor is closely related to patients' socioeconomic factors and their knowledge about the disease. ***Early palliative care*** may improve overall survival and patient-related outcomes in patients with advanced-stage lung cancer.
Underlying determinants: healthcare system and the availability of afatinib and gefitinib in Vietnam	***The healthcare system*** in Vietnam refers to health insurance, financial assistance, and social support for cancer patients. ***The availability of afatinib and gefitinib*** is a critical component of research conducted in Vietnam. Both agents are covered by Vietnamese health insurance, with a reimbursement of 50%.

CHAPTER 2. METHODOLOGY AND RESEARCH DESIGN

2.1. Methodology

Quantitative research

2.2. Research method

Retrospective combined with prospective digital medical record review. This is a valuable method for assessing treatment efficacy in a real-world setting due to several reasons:

Firstly, it ensures comprehensive data collection by collecting information from both past (retrospective) and ongoing (prospective) patient records, provides a more thorough understanding of medical histories, treatment progress, and outcomes.

Secondly, it demonstrates cost and time effectiveness as it uses existing medical records instead of additional data collection efforts.

Thirdly, it incorporates a real-world context by utilizing medical records derived from actual clinical environments. Furthermore, it enables the assessment of both short-term and long-term treatment effects and safety profiles over time.

Importantly, this research method adheres to ethical considerations by solely utilizing existing data without intervening or conducting any procedures on the patients. This ethical approach respects patient privacy and avoids subjecting individuals to additional interventions solely for research purposes.

In summary, the combined retrospective and prospective medical record review method provides a more holistic, ethical, and practical approach to evaluating treatment efficacy in real-world settings.

2.3. Research design

2.3.1. Study population and data collection

The study aimed at 80 patients with advanced-stage NSCLC with EGFR mutation-positive at the Department of Respiratory Medicine - 108 Military Central Hospital. All data were collected according to a unified research medical record form, and information was obtained from digital medical records.

2.3.2. Study duration and location

Study duration: from October 2022 to December 2023

Study location: 108 Military Central Hospital

2.3.3. Inclusion criteria

(1) patients with stage IIIB, IIIC, and IV NSCLC or recurrence after radical surgery

(2) documented EGFR mutation-positive including a deletion in exon 19 and the L858R point mutation in exon 21.

(3) patients > 18 years old

(4) had received no prior systemic treatment for advanced NSCLC

(5) duration of treatment was at least 3 months at the time of data analysis

(6) patients provided consent for treatment with gefitinib or afatinib

(7) sufficient information on treatment was available

2.3.4. Exclusion criteria

(1) patients with stage I, II, and IIIA NSCLC

(2) patients with small cell lung cancer

(3) previous or concomitant malignancies at other sites

(4) patients who did not provide consent for treatment with gefitinib or afatinib

(5) inadequate organ function as defined by the following criteria:

- Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≥ 3 x upper limit of normal (ULN), or AST and ALT ≥ 5 x ULN if liver function abnormalities are due to underlying malignancy.

- Total serum bilirubin ≥1.5 x ULN.

- Absolute neutrophil count (ANC) ≤ 1.5 x 109/L.

- Creatinine clearance < 45ml/min.

- Platelets ≤ 75 x 10^9/L.

2.4. Research flow chart

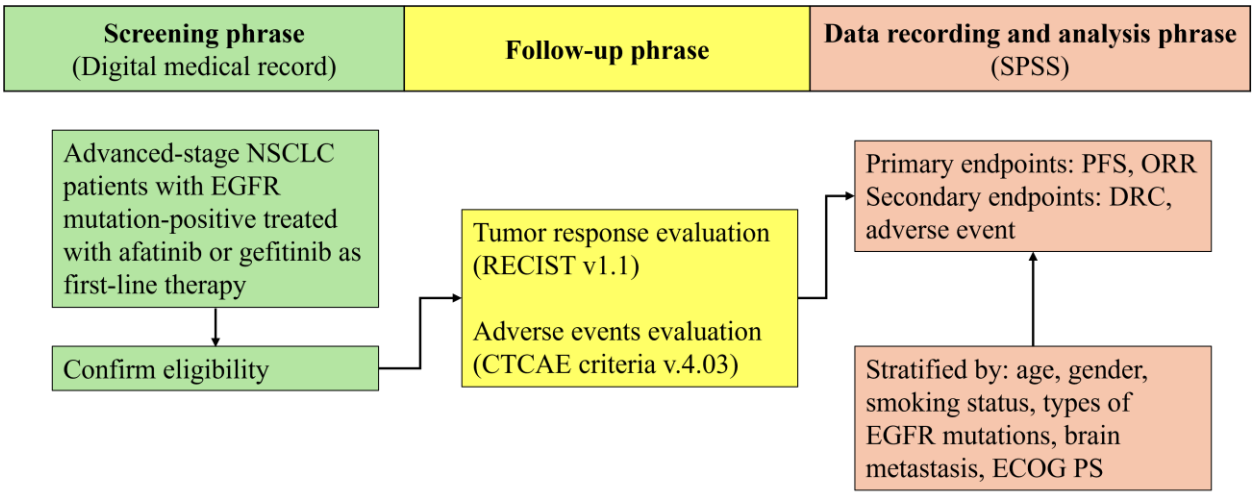


Figure 2.1. Research flow chart

2.4.1. Screening Phase

In the initial Screening phase, all patient data was collected from the digital medical records of individuals undergoing treatment at the Respiratory Department of Military Central Hospital 108. This encompassed both inpatient and outpatient records.

The objective of this screening was to identify advanced-stage NSCLC patients with EGFR mutation-positive and were treated with either afatinib or gefitinib as their first-line therapy. Patients meeting the study's inclusion criteria were then included in the subsequent phases of the research.

2.4.2. Follow-up Phase

The Follow-up phase consisted of the assessment of tumour response using the RECIST Response Evaluation Criteria in Solid Tumors (RECIST criteria) [59]. These criteria provided a framework for categorising patients' responses to treatment as follows:

Complete response	All lesions disappear after treatment
Partial response	A decrease of more than 30% in the total diameter of the lesions being treated
Progressive disease	An increase of 20% or more in the total diameter of the treated lesions or the appearance of new lesions
Stable disease	Criteria for progressive disease or partial response are not met

Additionally, the Follow-up phase involved an evaluation of adverse events using the Common Terminology Criteria for Adverse Events (CTCAE criteria) [60].

2.4.3. Data Recording and Analysis Phase

In the final Data Recording and Analysis phase, the SPSS was used for data collection and analysis. The data was stratified based on several factors, including age, gender, smoking status, types of EGFR mutations, the presence of brain metastasis, and Eastern Cooperative Oncology Group Performance Status (ECOG PS).

Two co-primary endpoints consist of the Objective Response Rate (ORR), Progression-Free Survival (PFS).

Two secondary endpoints encompass the Disease Control Rate (DCR) and adverse events.

PFS (Progression-Free Survival) is defined as the duration from the initiation of treatment to the date of disease progression or the date of death if the patient passed away earlier.

ORR (Objective Response Rate) refers to the proportion of patients within the study exhibiting a partial or complete response to the treatment within a specified period.

Disease Control Rate (DCR) represents the percentage of patients with advanced cancer whose therapeutic intervention resulted in a complete response, partial response, or stable disease.

Adverse events indicate the side effects or undesired symptoms that manifest after medication intake.

2.5. Analytical strategy

Using statistical software SPSS 22.0. Compare the means using the t-student test. The difference was statistically significant with $p < 0.05$. The survival time was expressed by the Kaplan-Meier curve. Calculate the risk index for disease progression or death using the Cox equation.

2.6. Reliability

To achieve high reliability, we have implemented a protocol for data collection. This protocol ensures that all participants are treated equally, from the screening period and treatment phase to the post-treatment follow-up period.

Factors such as types of EGFR mutation, the presence of brain metastasis, age, performance status, and comorbidities which are immediate determinants of primary and secondary endpoints in this research, will also be reduced by analyzing them under subgroups.

To avoid bias in obtaining information from medical records, we used chart review [61]. Furthermore, in order to enhance the robustness and comprehensiveness of our research report, we incorporated the utilization of the STROBE (The Strengthening the Transparent Reporting of Observational Studies in Epidemiology) checklist as a recommended research reporting guideline specifically designed for observational studies [62].

2.7. Ethics

In this study, ethical approval was obtained from the Ethics Committee of the 108 Military Center Hospital. Participants are unlikely to be physically or biologically harmed because of this study.

For every participant, a consent form will be provided. They will also be informed of the prerequisites for participation in the study and any possible risks and advantages. Participants will also be informed that any data they provide will be kept private and confidential, will only be used for the purpose of the study, and will not be shared with any other parties. Participants can also withdrawal from their consents at any time during the course of the study.

CHAPTER 3. RESULTS

The study encompassed 81 patients with advanced-stage NSCLC harboring EGFR mutations, treated at Military Central Hospital 108 from January 2019 to September 2022. These patients were split into two cohorts: 39 received Afatinib, while 42 were administered Gefitinib. Our findings from this investigation are as follows:

3.1. Baseline demographics, and disease characteristics

3.1.1. Age, gender and smoking status

Table 3.1. Distribution of patients by age, gender, and smoking status

Characteristics		Afatinib		Gefitinib		p
		N	%	N	%	
Average Age		**61.9±9.4**		**65,5±11,1**		0.12
Age Classification	**< 75 y/o**	38	97.4	34	88.9	0.018
	≥ 75 y/o	1	2.6	8	19.0	
Gender	**Male**	28	71.8	28	66.7	0.62
	Female	11	28.2	14	33.3	
Smoking Status	**Yes**	27	69.2	27	64.3	0.64
	No	12	30.8	15	35.7	

Comment:

- The Afatinib group has an average age of 61.9±9.4 with 38 patients (97.4%) under 75 and 1 patient (2.6%) 75 or older, while the Gefitinib group's average age is 65.5±11.1 with 34 patients (88.9%) under 75 and 8 patients (19.0%) 75 or older. The statistical analysis shows a non-significant difference in the average ages of patients between the Afatinib and Gefitinib groups, with a p-value of 0.12. However, when categorizing patients into age groups (<75 years old and ≥75 years old), there is a statistically significant difference between the groups, demonstrated by a p-value of 0.018.

- For Afatinib, 28 males (71.8%) and 11 females (28.2%) were treated; for Gefitinib, 28 males (66.7%) and 14 females (33.3%) were treated. The p-value for the gender comparison is 0.62, suggesting no statistical significance in the difference in gender distribution between the two treatment groups.

- In the Afatinib group, 27 patients (69.2%) are smokers and 12 patients (30.8%) are non-smokers. In the Gefitinib group, there are also 27 smokers (64.3%) but slightly more non-smokers, with 15 patients (35.7%). The p-value of 0.64 indicates that the difference in smoking status proportions between the two groups is not statistically significant.

3.1.2. Genetic mutation type

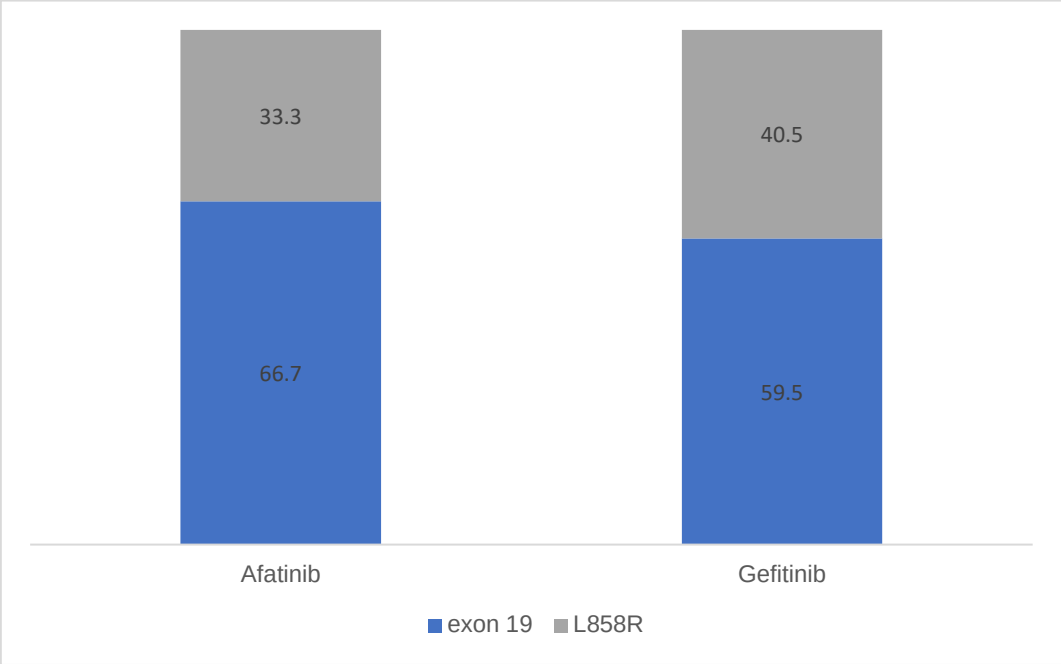


Chart 3.1. Distribution of patients by genetic mutation type

Comment:

For Afatinib, 26 patients (66.7%) have the exon 19 mutation and 13 patients (33.3%) have the L858R mutation. In the Gefitinib group, 25 patients (59.5%) have the exon 19 mutation, while 17 patients (40.5%) have the L858R mutation. The p-value is 0.51, indicating there is no significant statistical difference.

3.1.3. Brain metastasis at screening

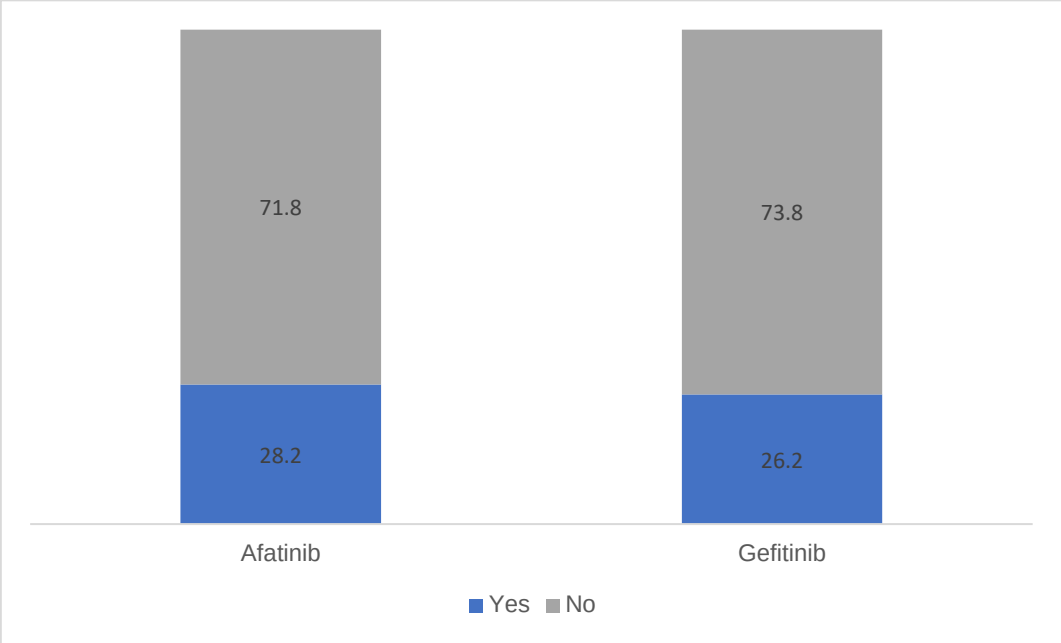


Chart 3.2. Distribution of patients by brain metastasis

Comment:

In the Afatinib group, 11 patients (28.2%) have brain metastasis, while 28 patients (71.8%) do not. The Gefitinib group has a similar distribution, with 11 patients (26.2%) having brain metastasis and 31 patients (73.8%) without. The p-value of 0.84 suggests there is no statistically significant difference.

3.1.4. ECOG

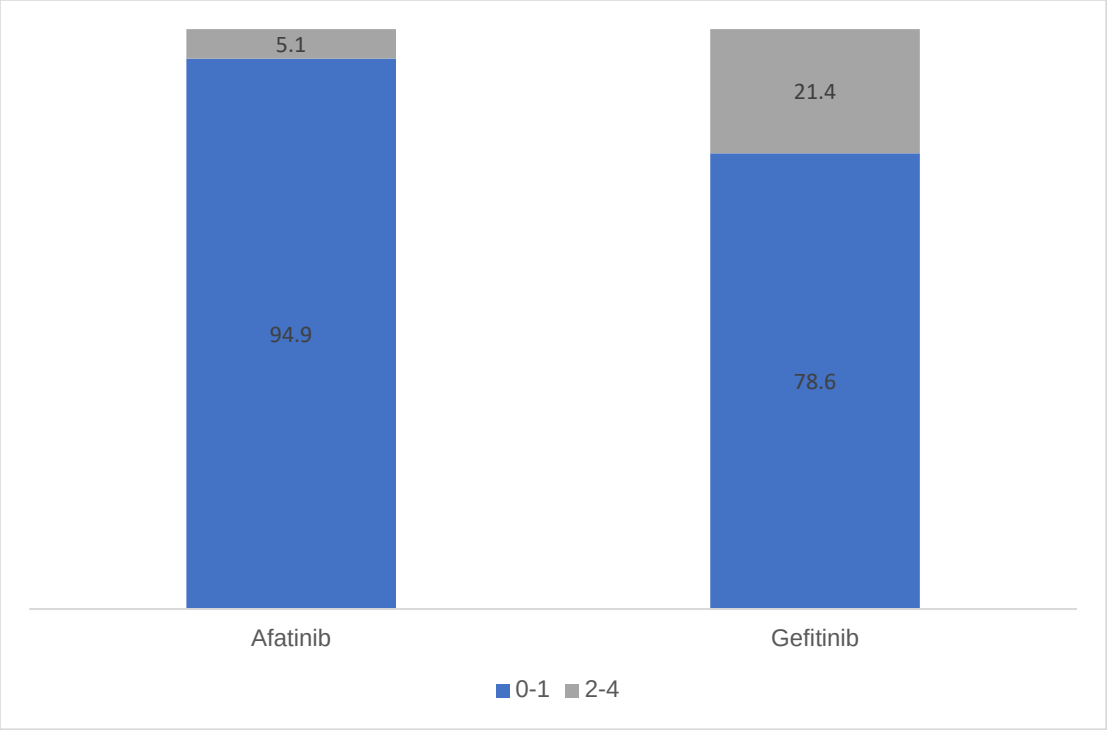


Chart 3.3. Distribution of patients by ECOG

Comment:

In the Afatinib group, 37 patients (94.9%) have a performance status of 0-1, indicating they are fully active or restricted in physically strenuous activity, while 2 patients (5.1%) have a status of 2-4, suggesting a greater degree of disability. Conversely, the Gefitinib group has 33 patients (78.6%) with a status of 0-1 and 9 patients (21.4%) with a status of 2-4. The p-value of 0.03 indicates a statistically significant difference between the two groups in terms of ECOG performance status.

3.2. Evaluation of treatment response

3.2.1. Treatment response

Table 3.2. Treatment response

Treatment response	Afatinib		Gefitinib		p
	n	%	n	%	
Complete response	6	15.4	7	16.7	>0.05
Partial response	31	79.5	25	59.5	
Disease stability	1	2.6	10	23.8	
Disease progression	1	2.6	0	0	
Objective response rate	37	94.9	32	76.2	0.02
Disease control rate	38	97.4	42	100	0.3

Comment:

For Afatinib, there were 6 cases (15.4%) of complete response, 31 cases (79.5%) of partial response, 1 case (2.6%) of disease stability, and 1 case (2.6%) of disease progression. In contrast, for Gefitinib, there were 7 cases (16.7%) of complete response, 25 cases (59.5%) of partial response, 10 cases (23.8%) of disease stability, and no cases (0%) of disease progression.

Afatinib demonstrated an objective response rate of 94.9% with 37 individuals responding, while Gefitinib had a lower rate of 76.2% with 32 individuals responding. The comparison is a statistically significant difference with a p-value of 0.02.

In terms of disease control rate, Afatinib showed a rate of 97.4% based on 38 cases, whereas Gefitinib displayed a slightly higher rate of 100% based on 42 cases. However, the p-value of 0.3 suggests that there was no significant difference between the disease control rates of the two treatments.

3.2.2. Objective response based on EGFR gene mutation type.

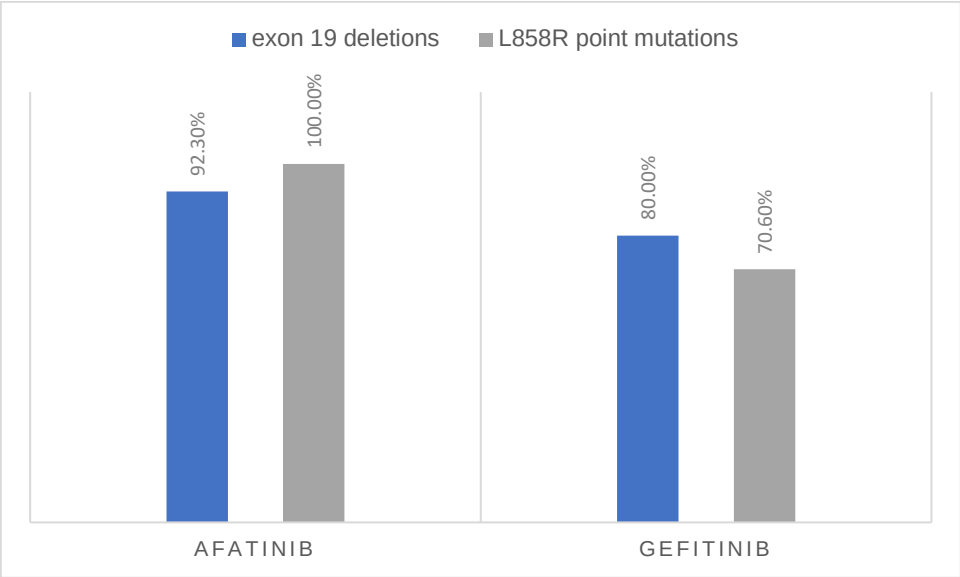


Chart 3.4. Objective response of Afatinib and Gefitinib based on EGFR gene mutation type.

Comment:

In patients exhibiting exon 19 deletions, the objective response rate (ORR) to treatment with afatinib is 92.3%, compared to 80% for those treated with gefitinib. This difference is not statistically significant, as indicated by a p-value of 0.2. Conversely, in the case of patients with L858R point mutations, the ORR is 100% for those treated with afatinib and 70.6% for patients receiving gefitinib. Here, the difference in ORR is statistically significant, as reflected by a p-value of 0.32.

3.3. Progression-Free Survival (PFS)

3.3.1. PFS of the Afatinib and Gefitinib Groups

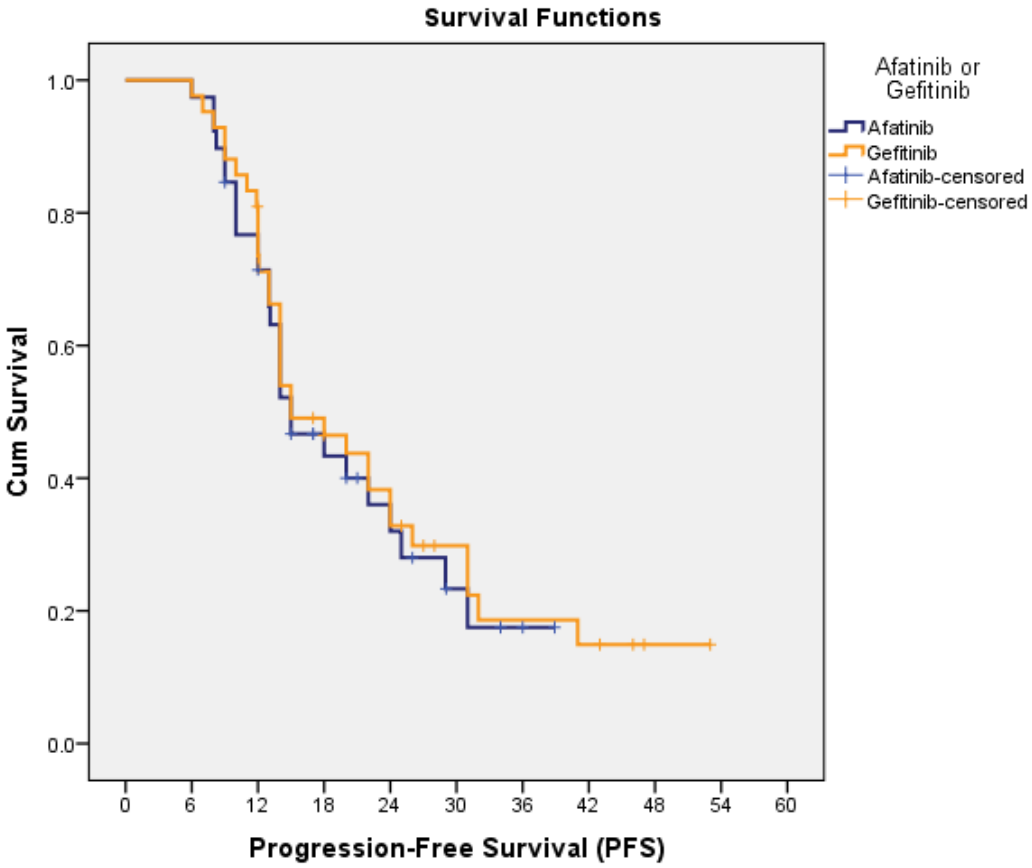
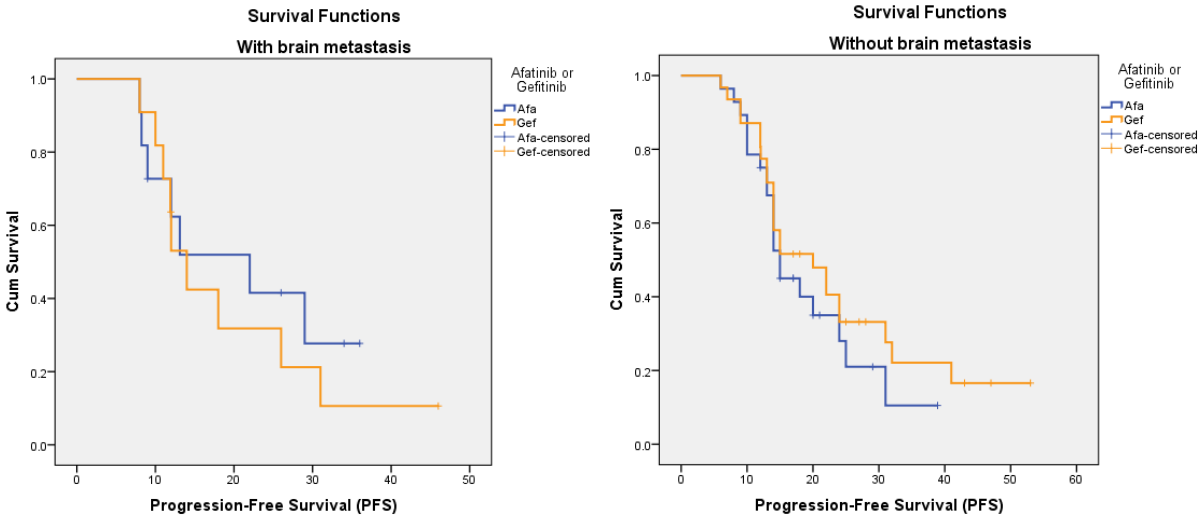


Chart 3.5. Progression-Free Survival of the Afatinib and Gefitinib groups

Comment:

The median PFS for patients treated with Afatinib was 15.0 ± 2.02 months (95% CI: 11.04 – 18.96). The median PFS for patients treated with Gefitinib was 15 ± 2.43 months (95% CI: 10.24 – 19.76), with no statistically significant difference at p=0.7. The 1-year and 2-year PFS rates for the Afatinib group were 71.4% and 32.0%, respectively, and for the Gefitinib group, they were 73.6% and 46.5%, respectively.

3.3.2. PFS based on Brain Metastasis and Non-Brain Metastasis



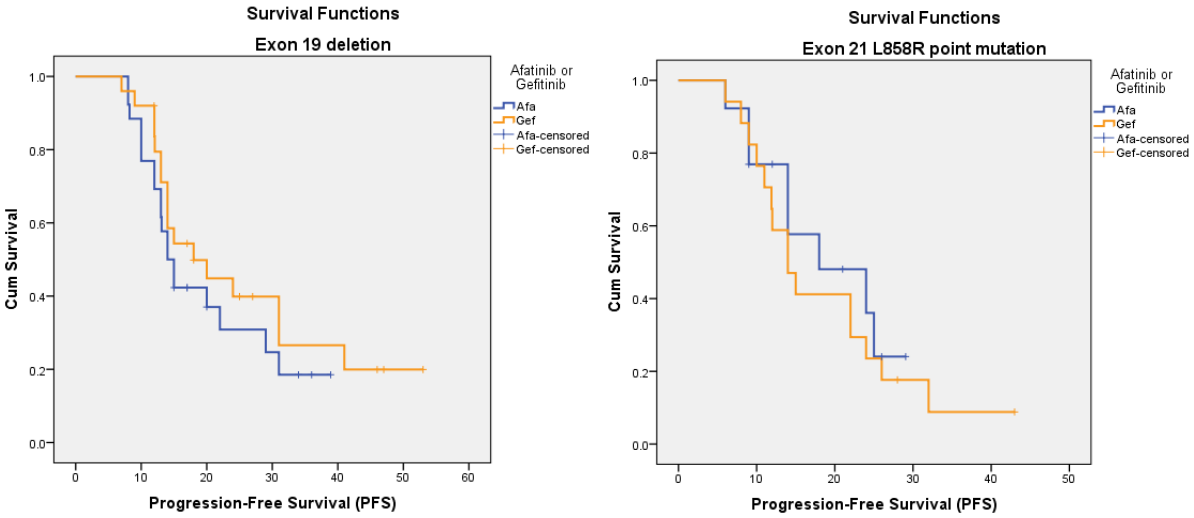
A **B**

Chart 3.6. Progression-free survival of patients treated with Afatinib and Gefitinib based on brain metastasis (A) and non-brain metastasis (B).

Comment:

For patients with brain metastasis, the median PFS for the Afatinib group was 22 ± 7.5 months (95% CI: 7.3 – 36.7 months), and for the Gefitinib group, it was 14 ± 1.5 months (95% CI: 10.9 – 17.0), p> 0.05. For patients without brain metastasis, the median PFS for the Afatinib group was 15 ± 0.9 months (95% CI: 13.3 – 16.7 months), and for the Gefitinib group, it was 20 ± 4.1 months (11.9 - 28.1 months), p> 0.05.

3.3.3. PFS based on Exon 19 Deletion and L858R Point Mutation



A **B**

Chart 3.7. Progression-Free Survival of patients treated with Afatinib and Gefitinib based on exon 19 deletion (A) and L858R point mutation (B)

Comment:

For patients with exon 19 deletion mutation, the median PFS for the Afatinib group was 14.0 ± 1.2 months (95% CI: 11.6 – 16.4 months), and for the Gefitinib group, it was 18 ± 4.5 months (95% CI: 9.2 – 26.8 months), p> 0.05. For patients with L858R point mutation, the median PFS for the Afatinib group was 18.0 ± 6.9 months (95% CI: 4.4 – 31.6 months), and for the Gefitinib group, it was 14 ± 2.1 months (95% CI: 9.9 – 18.0 months), p> 0.05.

3.4. Treatment-related adverse events

3.4.1. Treatment-related adverse events in general

Table 3.3. Treatment-Related Adverse Events in general

Adverse Effects	Afatinib or Gefitinib				
	Afatinib		Gefitinib		p
	n	%	n	%	
Yes	32	82.1	21	50.0	0.02
No	7	17.9	21	50.0	

Comment:

In the Afatinib group, 82.1% reported adverse effects, while 17.9% did not. For those on Gefitinib, adverse effects were reported by 50.0%, with an equal percentage not experiencing adverse effects. The p-value of 0.02 suggests a statistically significant difference in the rate of adverse effects between the two drugs.

3.4.2. Skin rash

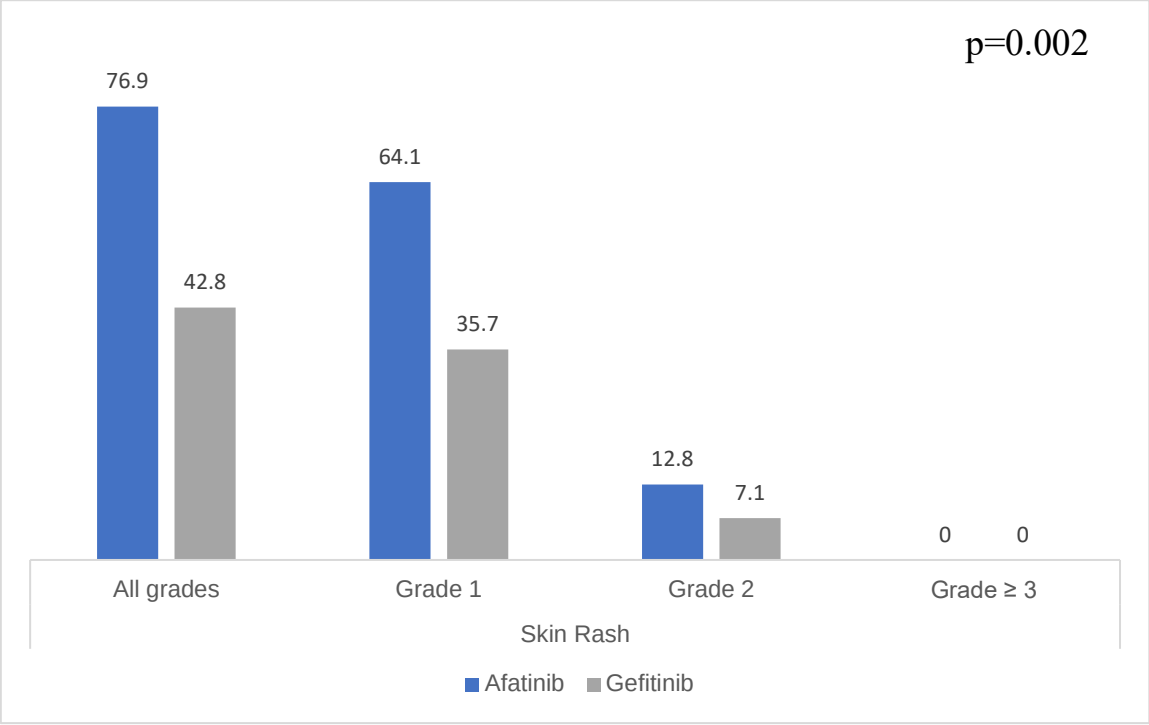


Chart 3.8. Skin rash (%)

Comment:

Of those on Afatinib, 76.9% experienced a skin rash of any grade, with 64.1% at Grade 1 and 12.8% at Grade 2; there were no cases of Grade ≥3. For Gefitinib users, 42.8% had a skin rash of any grade, with 35.7% at Grade 1 and 7.1% at Grade 2, again with no cases of Grade ≥3. The p-value of 0.002 indicates a statistically significant difference in the occurrence of skin rash between the two medications.

3.4.3. Diarrhea

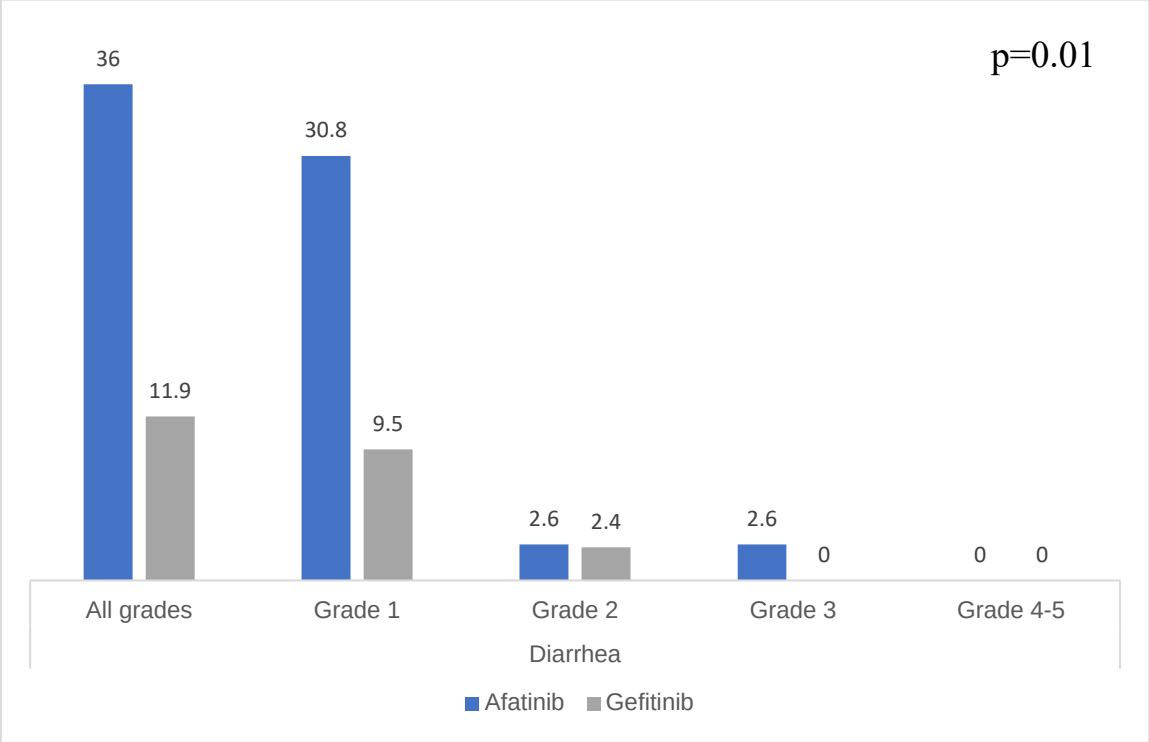


Chart 3.9. Diarrhea (%)

Comment:

In the Afatinib group, diarrhea was reported by 36% of patients across all grades: 30.8% had Grade 1, 2.6% had Grade 2, and another 2.6% experienced Grade 3, with no reports of Grade 4-5. Comparatively, in the Gefitinib group, 11.9% of patients experienced diarrhea across all grades, with 9.5% in Grade 1 and 2.4% in Grade 2, and no cases of Grade 3 or Grade 4-5. The p-value of 0.011 indicates a statistically significant difference in the incidence of diarrhea between the two treatments.

3.4.4. Other treatment-related adverse events

Table 3.4. Another treatment-related adverse events

Adverse Effects		Afatinib		Gefitinib		p
		n	%	n	%	
Nail inflammation	All grades	10	25.6	1	2.4	0.002
	Grade 1	7	17.9	0	0	
	Grade 2	3	7.7	1	2.4	
	Grade ≥ 3	0	0	0	0	
Elevated Liver Enzymes	All grades	0	0	0	0	Not applicable
	Grade 1	0	0	0	0	
	Grade 2	0	0	0	0	
	Grade ≥ 3	0	0	0	0	

Comment:

For nail inflammation, 25.6% of the Afatinib group experienced this effect at any grade, with 17.9% at Grade 1, and 7.7% at Grade 2; there were no cases reported for Grade ≥3. Only 2.4% of the Gefitinib group reported nail inflammation, all at Grade 2. There were no cases of elevated liver enzymes in any grade for either group. The p-value for nail inflammation is 0.002, indicating a statistically significant difference between the two drugs for this adverse effect.

CHAPTER 4. DISCUSSION

4.1. Patient and disease characteristics at baseline

4.1.1. Age, gender, and smoking status

Regarding the age distribution, our study primarily involved older persons (defined as those aged over 60, according to the United Nations [63]). The average age in the Afatinib-treated group was 61.9, whereas in the Gefitinib-treated group, it was 65.5. Although there was a trend for patients in the Gefitinib group to be older than those in the Afatinib group, this difference in average age did not reach statistical significance between the two groups. Similar trends were observed in other retrospective studies, where patients in the Gefitinib group tended to have a higher average age compared to those treated with Afatinib [52].

Moreover, in this study, we classified patient ages into two groups: one below 75 years old and another comprising patients aged 75 or above. Previously identified as a relevant cutoff, age 75 indicates a point where therapies deemed more effective and tolerable than chemotherapy are required [64, 65]. Consequently, the percentage of patients aged 75 or above in the Gefitinib group was 19.0%, higher than the 2.6% observed in the Afatinib group, with a statistically significant difference of $p=0.018$. This observation suggests that for elderly patients, physicians tend to favour Gefitinib over Afatinib due to its perceived safety, a trend noted in several other studies [52, 66].

Additionally, our study predominantly involved male patients with a history of smoking. These characteristics align with common traits observed in current research on lung cancer in Vietnam [5, 67].

4.1.2. Distribution of patients by genetic mutation type

In this study, we specifically enrolled patients with documented EGFR mutation-positive status, including the presence of a deletion in exon 19 and the L858R point mutation in exon 21. These two EGFR mutations are among the most common mutations in NSCLC patients [28]. Our study findings reveal a higher incidence of EGFR exon 19 deletion mutations compared to the L858R point mutation in both patient groups. Similar results have been reported in studies examining the spectrum of EGFR gene mutations among NSCLC patients in both Vietnam and globally [5, 55, 68].

4.1.3. Distribution of patients by brain metastasis

In this study, both the Afatinib and Gefitinib treatment groups exhibited similar rates of brain metastasis at the beginning of treatment (28.2% in the Afatinib group and 26.2% in the Gefitinib group, p=0.84). These rates were higher than those reported in the Lux-Lung 7 study, which indicated approximately 16% and 15% for brain metastasis at diagnosis in the Afatinib and Gefitinib treatment groups, respectively [68]. However, the incidence of brain metastasis in our study aligns with findings from another research. According to Hendriks, L.E., et al., at the initial diagnosis of metastatic NSCLC, brain metastases were present in 25.0-52.0% of patients. This incidence varied among three groups with different mutations, but the differences were not statistically significant [69].

4.1.4. Distribution of patients by ECOG

The Afatinib group showed a higher proportion of patients with ECOG scores of 0-1, while the Gefitinib group had a significantly more significant percentage of patients with ECOG scores of 2-4. This difference in performance status between the groups was statistically significant, with a p-value of 0.03. This observation suggests that for older patients with higher ECOG scores, physicians tend to prefer Gefitinib due to its perceived safety. Notably, this study analysed patients across all ECOG score categories, unlike Lux-Lung 7, which focused only on patients with ECOG scores of 0-1 [68].

4.2. Treatment response

4.2.1. Objective Response Rate (ORR)

In this study, the mean follow-up time was 24 months. We observed a similar complete response rate between the two groups (the Afatinib treatment group at 15.4% and the Gefitinib treatment group at 16.7%). Meanwhile, the partial response rate for Afatinib was 79.5%, higher than Gefitinib's 59.5%. Consequently, the ORR for the Afatinib group (94.9%) was higher than that for the Gefitinib group (76.2%), showing statistical significance with a p-value of 0.02. This trend was also noted in the Lux-Lung 7 study, where the ORR for the Afatinib group was 70%, surpassing the Gefitinib group's 56% with p = 0.0083 [68].

Analysis of objective response rates based on the position of the EGFR gene mutation revealed that Afatinib had higher response rates than Gefitinib for both exon 19 deletion and L858R mutations. In Lux-Lung 7, the ORR for exon 19 deletion mutations was 73% for Afatinib and 66% for

Gefitinib, while for patients with L858R mutations, these rates were 66% and 42%, respectively [68].

According to Vu Ha Thanh et al., the ORR was 75% in patients treated with Afatinib as first-line therapy for advanced stages NSCLC with EGFR mutation- positive. However, this evaluation occurred at the 8 to 12-week mark, which may not fully reflect the response rate throughout the treatment duration. The response rate might increase further in subsequent cycles for patients stabilizing or achieving partial or complete responses. Subgroup analysis indicated an ORR of 78.9% for patients with exon 19 deletion mutations and 87.5% for those with L858R mutations. Additionally, disease control rates reached 100% in both exon 19 deletion and L858R mutation patient groups in this study [5].

4.2.2. Disease control rates (DCR)

In terms of DCR, our study indicated almost equivalent effectiveness of both drugs, with Afatinib showing a 97.4% DCR and Gefitinib 100%, and a non-significant p-value of 0.3. These findings align closely with the findings of both the Lux-lung 7 study and Haaland B. et al.'s research [68, 70]. The Lux-lung 7 study found that the DCR for the Afatinib group was 91% (146/160 patients) and 87% (139/159) for the Gefitinib group, with a p-value of 0.24 [68]. This suggests a slight advantage for Afatinib, but the difference was not statistically significant. Similarly, Haaland B. et al.'s study reported a pooled hazard ratio-estimate for Afatinib versus Gefitinib as 1.01 (95% CI, 0.53-1.92; 95% PI, 0.42-2.42), indicating comparable efficacy between the two drugs [70].

4.3. Progression-Free Survival (PFS)

Our assessment of PFS revealed that the median PFS for patients treated with Afatinib was 15.0 ± 2.02 months, comparable to the median PFS for those treated with Gefitinib at 15 ± 2.43 months, with no statistically significant difference observed. From the visual assessment of the progression-free survival curves of the Afatinib and Gefitinib groups, it seems that there is no dramatic difference in the progression-free survival between the two drugs over the time span observed. The curves are close together, and the p-value confirms that there is no statistically significant difference between the two treatments in terms of PFS.

This stands in contrast to the results presented by Park K. et al., which suggested that Afatinib treatment led to a longer median PFS compared to Gefitinib. This difference was statistically significant, with a p-value of 0.017 [68]. Moreover, A comprehensive meta-analysis by Haaland B. et al., which incorporated data from eight clinical trials on first-line tyrosine kinase inhibitor (TKI)

treatments, corroborates our findings. This analysis also demonstrated no significant difference in progression-free survival (PFS) between Afatinib and Gefitinib. Their study's pooled hazard ratio-estimate for Afatinib versus Gefitinib was 1.01, with a 95% confidence interval (CI) of 0.53-1.92 and a 95% prediction interval (PI) of 0.42-2.42 [70].

4.3.1. PFS based on Brain Metastasis and Non-Brain Metastasis

Among patients with brain metastasis, we noted a trend toward longer median PFS in the Afatinib group compared to the Gefitinib group, with median PFS values of 22 months and 14 months, respectively. Conversely, in patients without brain metastasis, the Gefitinib-treated group exhibited a longer median PFS, though not statistically significant. From the visual assessment of the progression-free survival curves of the patient group without brain metastasis, the overall shape of the curves suggests that patients without brain metastasis have a longer progression-free survival than those with brain metastasis. The curves for Afatinib and Gefitinib in this group are much closer together, indicating more similar PFS outcomes for the two drugs in the absence of brain metastasis. The difference was not statistically significant confirmed with $p>0.05$. Lux-Lung 7 study findings also indicated no difference in PFS between Afatinib and Gefitinib treatments in both brain metastatic and non-brain metastatic patients, with $p=0.93$ [68]. Another study by Tu C.Y. et al. similarly showed no difference in PFS among Afatinib, Gefitinib, and Erlotinib treatments in brain metastatic patients. However, in non-brain metastatic patients, Afatinib treatment demonstrated superior PFS compared to first-generation TKI treatments, with a statistical significance at $p=0.01$ [71]. These studies suggest that Gefitinib also holds efficacy in brain metastatic advanced NSCLC patients.

4.3.2. PFS based on Exon 19 Deletion and L858R Point Mutation

For patients with exon 19 deletion mutations, those treated with Afatinib exhibited a shorter median PFS compared to those receiving Gefitinib. Specifically, the median PFS for the Afatinib group was 14.0 ± 1.2 months (95% CI: 11.6 – 16.4 months), while for the Gefitinib group, it was 18 ± 4.5 months (95% CI: 9.2 – 26.8 months), with a p-value greater than 0.05. The Kaplan-Meier survival curves illustrate this trend: initially, the Afatinib curve is higher, indicating a better early response. However, after about 10 months, the curves cross, with Gefitinib showing superior PFS subsequently. Despite these trends, the difference in median PFS between the treatments for the exon 19 deletion group is not statistically significant, as indicated by a p-value over 0.05.

Conversely, for patients with the L858R mutation, a different pattern emerges. The median PFS for those on Afatinib exceeds that of the Gefitinib group: 18.0 ± 6.9 months (95% CI: 4.4 – 31.6 months) for Afatinib and 14 ± 2.1 months (95% CI: 9.9 – 18.0 months) for Gefitinib, also with a p-value greater than 0.05. The survival curves consistently show the Afatinib curve maintaining superiority throughout the observed duration.

In contrast, data from the Lux-lung 7 trial presents a different scenario. Here, the median PFS for patients treated with Afatinib was higher than for those treated with Gefitinib in both genetic mutation groups. The median PFS for the Afatinib group was 12.7 and 10.9 months, compared to 11.0 and 10.8 months for the Gefitinib group, for Exon 19 Deletion and L858R Point Mutation types, respectively. However, as in our study, the p-value exceeded 0.05, indicating no statistically significant difference between the two treatments in the Lux-lung 7 trial [68].

Furthermore, literature reviews, including studies by Kim Y. et al., report no significant difference in PFS between Afatinib and Gefitinib in patients with L858R mutations [52]. This is in line with findings from Tu C.Y. et al. and Su P.L. et al., which also conclude no PFS advantage when comparing Afatinib, Gefitinib, and Erlotinib across both exon 19 deletions and L858R mutations [53, 71]. These findings collectively suggest that while individual responses to EGFR-targeted therapies can vary, the median PFS may not differ significantly when considering broader patient populations.

4.4. Treatment-related adverse events

In our study, we found a lower overall incidence of adverse events, with fewer and less severe adverse events compared to previous research [68] [72]. According to the Lux-lung 7 study, up to 99% of patients in the Afatinib group and 100% in the Gefitinib group experienced side effects of any severity. The most common adverse events included diarrhea, rash or acne, stomatitis, paronychia, dry skin, fatigue, decreased appetite, nausea, alopecia, vomiting, and increased ALT/AST levels. In the Afatinib group, up to 31% of patients experienced severe (Grade 3 and 4) side effects, while in the Gefitinib group, up to 18% of patients experienced severe (Grade 3 or higher) side effects [68]. The difference in our study could be related to limitations commonly associated with retrospective studies and reliance on digital medical records.

Additionally, we observed that patients treated with Afatinib tend to experience a higher rate of treatment-related adverse effects than those on Gefitinib in general: 82.1% of the Afatinib group reported adverse effects, compared to 50.0% in the Gefitinib group. More specifically, our findings

indicate that Afatinib is associated with a statistically significant increase in the incidence of skin rash across all grades compared to Gefitinib. The most marked disparity was seen in Grade 1 skin rash, with Afatinib showing nearly double the incidence rate of Gefitinib. Despite the relatively high occurrence of skin rash with these drugs, the absence of Grade 3 rashes is encouraging, suggesting that while skin rashes are common, they rarely escalate to the most severe form.

Our research also shows that Afatinib is more closely linked to gastrointestinal side effects, as evidenced by the higher frequency of all grades of diarrhea among its users. The statistical significance of this difference is underscored by a p-value of 0.01. Particularly striking is the difference in mild diarrhea (Grade 1), where the rate for Afatinib is more than threefold that of Gefitinib. However, the incidence of moderate diarrhea (Grade 2) is similar for both drugs, implying a comparable risk for moderate severity. Notably, the occurrence of severe diarrhea (Grade 3) was observed only in the Afatinib group, albeit in a small percentage of patients. This finding, while limited to a small number of cases, could raise clinical concerns. The absence of the most severe levels of diarrhea (Grade 4-5) in our study indicates that although these medications can cause diarrhea, they typically do not result in the most extreme, life-threatening conditions.

Further, our observational study found a more frequent occurrence of paronychia in patients treated with Afatinib. In contrast, we did not encounter any instances of elevated liver enzymes, a side effect that is more commonly associated with Gefitinib treatment in other studies [6, 68].

To summarize, the evidence points to a higher incidence of treatment-related adverse events with Afatinib, reinforcing the need for comprehensive supportive care and thorough patient education about managing potential side effects. This is particularly crucial for those prescribed Afatinib, as the management of side effects is essential to ensure treatment adherence and maintain the patient's quality of life.

4.5. Limitations

Our research, which combined retrospective and prospective observational methods, was designed to assess the efficacy of two medications. Nevertheless, it encountered several limitations:

Sample Size Limitation: With a total of 81 participants, our study had a relatively modest sample size. This small cohort limits the statistical power of the research, particularly when it comes to detecting nuanced differences within subgroups.

Study Design Constraints: Since our study was not structured as a randomized controlled trial, it is susceptible to selection biases. These biases could have influenced which patients received certain treatments, potentially skewing the results and affecting the overall conclusions about the efficacy and safety of the medications.

Adverse Event Reporting Issues: Although we documented the severity of adverse events, there is a possibility that some events were underreported or that inconsistencies existed in the reporting process. This could lead to an incomplete understanding of the drugs' safety profiles.

Generalizability Concerns Due to Single-Center Setting: The fact that this study was conducted at a single centre raises concerns regarding the external validity of the findings. Results from a single institution may not be universally applicable, given the variability in patient populations and practice patterns across different centres.

Duration of Follow-Up: The follow-up period in our study was relatively short, which might not allow for the observation of adverse effects that emerge later or the full scope of the medications' long-term efficacy and safety.

In response to these limitations, future studies should be planned to include larger sample sizes and longer follow-up durations. These efforts aim to enhance the robustness of the findings and ensure that they more accurately reflect the medications' performance in a real-world, diverse patient population. Additionally, measures will be taken to improve the rigor of adverse event reporting and to expand the study to multiple centers, thereby strengthening the generalizability of the results.

CONCLUSION

1. Either afatinib or gefitinib can be used for patients with brain metastasis.

2. In general, the treatment response of afatinib is superior to that of gefitinib. However, adverse events were significantly higher in the Afatinib group but manageable.

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THESIS/DISERTATION SUBMISSION FORM

Surname	Middle name	First name	Title (Eg. Mr., Ms., Miss., etc.)
Nguyen	*Dinh*	*Tung*	*Mr*

Student number : V202000310	**Graduation in:**
Permanent email address : *tungk45hnue@gmail.com*	Should your email address be made available on the Vinspace website (circle the answer)? **YES** | **NO**
Telephone number: *+ (84) 987 690481*	
College : *College of Health Sciences*	**Major: Internal Medicine**
Degree: *Bác sĩ nội trú*	
Supervisor(s) : Pham Van Luan, M.D, PhD	
Title of the study: **The efficacy of afatinib and gefitinib as first-line therapy in advanced-stage non-small cell lung cancer (NSCLC) with EGFR mutation-positive in Vietnamese patients**	
Document type (thesis or dissertation): Thesis	
Please supply 5 keywords for the study (Use subject heading from https://authorities.loc.gov/):	**1. Non-small-cell lung cancer** **2. EGFR mutation** **3. Afatinib** **4. Gefitinib** **5. Vietnamese**

Abstract/Summary

Background: In Vietnam, Afatinib and Gefitinib are two commonly prescribed TKIs for treating advanced-stage non-small cell lung cancer (NSCLC) patients with EGFR mutation-positive. However, to our knowledge, no comparative studies on the treatment efficacy of these two drugs have been conducted among the patient population in Vietnam.

Objective: This research aims to compare the treatment efficacy of Afatinib and Gefitinib in advanced-stage NSCLC patients with EGFR mutation-positive in Vietnam.

Methods: This is a prospective combined with retrospective cohort study. The study included 81 advanced-stage NSCLC patients with EGFR mutation-positive, treated with either Afatinib or Gefitinib from January 2019 to September 2022 at the Respiratory Department – Military Central Hospital 108. Patient information was collected from digital medical records to assess primary outcomes, including progression-free survival (PFS), objective response rate (ORR), secondary outcomes such as disease control rate (DCR), and adverse events.

Main findings: This research involved 81 patients with advanced-stage NSCLC with EGFR mutations; 39 received Afatinib (average age 61.9±9.4) and 42 Gefitinib (average age 65.5±11.1). The prevalence of brain metastasis was nearly the same in both groups, 28.2% in the Afatinib group and 26.2% in the Gefitinib group. Median PFS was comparable: median PFS for the Afatinib group was 15.0 ± 2.02 months (95% CI: 11.04 – 18.96), and for the Gefitinib group, it was 15 ± 2.43 months (95% CI: 10.24 – 19.76), with no significant difference (p=0.7). However, ORR was significantly higher in the Afatinib group at 94.9% compared to 76.2% in the Gefitinib group, with a statistically significant p-value of 0.02. DCR was 97.4% in the Afatinib group and 100% in the Gefitinib group, but this difference was not statistically significant (p=0.3). Notably, the incidence of adverse effects was significantly higher in the Afatinib group (82.1%) compared to the Gefitinib group (50%), with a p-value of 0.02. Most adverse events were mild, classified as grade 1 or 2.

Conclusion: In general, the treatment response of afatinib is superior to that of gefitinib. However, adverse events were significantly higher in the Afatinib group but manageable.

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SIGNATURE OF STUDENT: Nguyen Dinh Dung
DATE: 30/11/2024

LIST OF RESEARCH PARTICIPANTS

Resident name: NGUYEN DINH TUNG ID: 202000310

Residency Program: Internal Medicine

Thesis title: The efficacy of Afatinib and Gefitinib as first-line therapy in advanced-stage non-small cell lung cancer (NSCLC) with EGFR mutation-positive

No	Name	Date of birth	Patients ID	Address
1	Nguyen Quoc B	1961	20151650	Phu Tho
2	Dao Van Khai	1945	18317288	Ha Noi
3	Nguyen Thi H	1948	19197970	Nam Dinh
4	Do Thi C	1987	19013452	Quang Ninh
5	Tran Van B	1960	17356954	Nam Dinh
6	Nguyen Thac M	1951	20141774	Bac Ninh
7	Bui Trung T	1963	15174037	Ha Noi
8	Do D	1949	20136958	Thai Binh
9	Pham The T	1971	20198118	Thanh Hoa
10	Mac Thi L	1958	20321189	Hai Duong
11	Le Xuan P	1949	20275268	Thanh Hoa
12	Pham Van C	1949	20356287	Nam Dinh
13	Duong Van C	1960	18038310	Ha Noi
14	Le Minh H	1955	20146907	Thanh Hoa
15	Trinh Ngoc H	1964	20376702	Thanh Hoa
16	Dinh Thi P	1960	20461405	Quang Ninh
17	Duong Duy L	1947	16343283	Ha Noi
18	Nguyen Van T	1954	20396506	Hai Duong
19	Do Ngoc O	1952	14003696	Ha Noi
20	Luu Cong T	1977	20013766	Ha Noi
21	Nguyen Luong T	1964	20558729	Ha Noi
22	Bui Tien H	1956	20729667	Ha Noi
23	Trinh Ngoc T	1970	20800103	Ha Noi
24	Nguyen Van N	1951	13305644	Ha Noi
25	Vu Thi T	1950	20962816	Ha Noi
26	Vu Tien L	1961	21018700	Thai Binh
27	Nguyen Thi N	1950	21139961	Ha Nam
28	Luu Thuy N	1977	21051054	Ha Noi
29	Dang Thi Minh C	1957	19401037	Ha Noi
30	Nguyen Huy P	1947	20926102	Hai Duong
31	Truong Van N	1973	21137709	Thanh Hoa
32	Hoang Dinh H	1964	20802562	Hai Phong

33	Huu Thi T	1955	21250121	Thanh Hoa
34	Nguyen Quoc C	1967	21317081	Hung Yen
35	Nguyen Thi Tuyet M	1963	18227300	Ha Noi
36	Tran Thi H	1952	21475323	Hai Phong
37	Nguyen Quang M	1955	21345441	Ha Noi
38	Duong Van K	1955	19459064	Ha Noi
39	Pham Thi T	1939	20698237	Ha Noi
40	Nguyen Thi P	1954	19451940	Hai Phong
41	Tran Thi Q	1948	19351876	Hung Yen
42	Loc Thi H	1971	20843942	Vinh Phuc
43	Nguyen Thi C	1972	22034241	Ha Noi
44	Trinh Thi H	1962	19584214	Ha Noi
45	Phung Van B	1940	21137477	Phu Tho
46	Nguyen Van D	1947	14315989	Ha Noi
47	Trinh Thanh T	1986	21502703	Thanh Hoa
48	Tran Ngoc Y	1948	14093925	Ha Noi
49	Pham Thanh T	1953	19060732	Ha Noi
50	Le Thi Minh L	1939	18149289	Ha Noi
51	Tran Quang L	1946	19005670	Hai Phong
52	Nguyen Thi U	1954	20795639	Hai Duong
53	Bui T B	1974	20351768	Quang Ninh
54	Le Van V	1963	18236506	Quang Binh
55	Nguyen Van P	1958	20764073	Hai Phong
56	Pham Thi D	1962	21146708	Ha Noi
57	Do Van N	1959	20626046	Bac Ninh
58	Nguyen Phi K	1962	20174789	Ha Nam
59	Doan Trong G	1959	20748019	Ha Noi
60	Duong Thi N	1948	18205730	Ha Noi
61	Vu Dang D	1952	18558801	Ha Noi
62	Bui Xuan K	1947	20555081	Nam Dinh
63	Le Huy M	1943	20780722	Ha Noi
64	Hoang Quoc T	1960	22187062	Quang Ninh
65	Pham Van T	1971	21067133	Hai Duong
66	Nguyen Thi B	1958	18143473	Ha Noi
67	Pham N	1940	22150091	Thai Binh
68	Dang Van D	1960	17343385	Ha Noi
69	Chu Van D	1949	21325974	Ha Nam
70	Nguyen Van C	1965	21388825	Bac Ninh
71	Vu Thi D	1953	21280274	Ha Nam
72	Doan Huy T	1959	16439812	Hai Phong

73	le Thanh L	1977	20657574	Bac Ninh
74	Pham Van V	1950	19308761	Nam Dinh
75	Nguyen Dinh H	1962	16437042	Thai Binh
76	Nguyen Van P	1960	21489851	Thanh Hoa
77	Vu Minh D	1963	21671993	Ha Noi
78	Hoang Thi H	1945	21409053	Thai Nguyen
79	Nguyen Hong T	1942	20100854	Hoa Binh
80	Nguyen Thanh H	1936	21442102	Son La
81	Dao Van M	1954	20609925	Hung Yen

108 MILITARY CENTRAL HOSPITAL CONFIRMED:

Doctor. Nguyen Dinh Tung conducted the project: "The efficacy of Afatinib and Gefitinib as first-line therapy in advanced-stage non-small cell lung cancer with EGFR mutations positive" on 81 patients listed at 108 Military Central Hospital, with the academic advisor of Dr. Pham Van Luan - Department of Respiratory Medicine, 108 Military Central Hospital.

The hospital agreed to allow Dr. Nguyen Dinh Tung to use relevant data in the medical record to publish in the project.

Hanoi, January 12, 2024

Academic supervisor

Pham Van Luan, MD, PhD

Confirmation from research facility
108 Military Central Hospital

KT. GIÁM ĐỐC
PHÓ GIÁM ĐỐC

Thiếu tướng Lâm Khánh

APPENDIX B - STROBE Statement

Checklist of items that should be included in reports of observational studies.

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	30
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	31
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	31

		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	28
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	33-35
Bias	9	Describe any efforts to address potential sources of bias	35
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	33-35
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	35
		(b) Describe any methods used to examine subgroups and interactions	

		(c) Explain how missing data were addressed	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	33
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	37
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	53

Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	42-50
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	42-50
Discussion			
Key results	18	Summarise key results with reference to study objectives	51-59
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	59-60

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	51-60
Generalisability	21	Discuss the generalisability (external validity) of the study results	60
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

N/A: Not available/ Not applicable

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.