RESEARCH ARTICLE

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Treatment Patterns and Survival Outcomes in a Real-World Cohort of 263 Patients with EGFR L858R-Mutant Non-Small Cell Lung Cancer: Focus on EGFR-TKI Selection

Vinh Hung Pham[1], Huyen Nga Do[2], Khanh Toan Nguyen[3], Lam Van Ngo[3]*, Thi Huong Pham[3], Thi Hong Anh Vo[3], Thi Thuy Phan[3], Thi Thu Hien Tran[3], Thi My Hanh Tran[3], Thi Thuy My Nguyen[3], Van Thanh Le[3], Thi Hai Yen Le[3], Tuan Trung Tran[3], Khanh Hung Truong[3]

Abstract

Aim: Compare the treatment efficacy of EGFR TKIs in patients with non-small cell lung cancer with the EGFR L858R exon 21 mutation. **Materials and methods:** This retrospective analysis included 263 patients with advanced non-small cell lung cancer harboring the EGFR L858R mutation who were treated with EGFR tyrosine kinase inhibitors (TKIs) at Nghe An Oncology Hospital, Vietnam, between January 2018 and June 2025. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. The association of clinical factors with survival outcomes was assessed using Cox proportional hazards regression models. **Results:** The median progression-free survival (PFS) and overall survival (OS) for the study population were 14.1 months and 24.9 months, respectively. In the entire population (n=263), osimertinib demonstrated superior efficacy compared to first-and second generation EGFR TKIs (PFS: HR = 0.37, 95% CI: 0.21-0.63, p < 0.001; OS: HR = 0.31, 95% CI: 0.15-0.63, p = 0.001). In multivariate analyses (n = 232), afatinib was not associated with a statistically significant improvement in survival outcomes compared to first generation EGFR TKIs (PFS: HR = 0.70, 95% CI: 0.43–1.13, p = 0.143; OS: HR = 0.71, 95% CI: 0.42–1.19, p = 0.199). Subgroup analysis showed that the benefits of osimertinib were maintained in patients with malignant pleural effusion (PFS: HR = 0.40, 95% CI: 0.16-0.95, p = 0.040; OS: HR = 0.31, 95% CI: 0.11-0.87, p = 0.027). **Conclusions:** In patients with the EGFR L858R exon 21 mutation, our real-world data demonstrate that osimertinib is the most effective TKI, while afatinib offers no significant survival advantage over first-generation TKIs. This underscores the importance of mutation-specific treatment strategies.

Keywords: Non-small cell lung cancer- EGFR L858R- EGFR TKI- Vietnam

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Introduction

In Vietnam, the rate of EGFR gene mutations is approximately 40%. The EGFR L858R mutation in exon 21 accounts for over one-third of these cases [1]. While there are many specific drugs available for this patient group, the commonly used drugs in our country include Erlotinib, Gefitinib, Afatinib, and Osimertinib.

Previous studies typically evaluate the therapeutic efficacy of targeted agents on both the L858R exon 21 and del exon 19 subtypes [2, 3]. Therefore, the overall view of treatment efficacy in patients with specific gene mutations is not really optimal. Additionally, the EGFR L858R exon 21 mutation is associated with a poorer prognosis than the EGFR Del exon 19 mutation [4, 5].

Research indicates that combining antiangiogenic drugs with EGFR-targeted therapies leads to improved outcomes for patients with the L858R mutation [6]. However, the toxicity and cost of treatment are important factors that must be carefully considered. Specifically, health insurance in our country does not fully cover these medications. As a result, the use of single-targeted drugs remains the most common practice in clinical settings.

Although benefiting from targeted therapy, special subjects such as those with brain metastases or pleural fluid metastases often have a poor prognosis [7]. Selecting the appropriate treatment for these patients is crucial due to their high tumor burden and severe symptoms, which

*[1]Nghe An Oncology Hospital, Nghe An, Vietnam. [2]Department of Hematologic Oncology, Vietnam National Cancer Hospital, Ha Noi, Viet Nam. [3]Department of Medical Oncology 2, Nghe An Oncology Hospital, Nghe An, Vietnam. *For Correspondence: Drlam.ubna@gmail.com*

significantly impact their quality of life. However, real-world data on optimizing treatment for these two specific patient groups is quite limited.

Our study aims to thoroughly evaluate the effectiveness of all three generations of targeted drugs in patients with advanced non-small cell lung cancer who have the EGFR L858R exon 21 mutation. We will focus particularly on individuals with brain metastases and pleural fluid metastases, assessing outcomes in the context of real-world clinical practice.

Materials and Methods

Study locations and patients

This study was conducted at Nghe An Oncology Hospital from January 2018 to June 2025. This is the largest specialized oncology hospital in the central region of Vietnam.

Patient selection criteria

1. Age > 18 (years)
2. Non-small cell lung cancer stage III, IV according to the AJCC 8th, 2017
3. EGFR L858R exon 21 mutation positive (Realtime PCR or NGS)
4. Treated with EGFR TKIs (Erlotinib, Gefitinib, Afatinib, Osimertinib)
5. The lesions were evaluated using the RECIST 1.1 criteria established in 2009.
6. Full archives

Exclusion criteria:

1. Have multiple cancers occurring simultaneously.

Study design and size samples

This was a retrospective observational study. We recruited 263 patients who met the inclusion criteria for analysis. Patients undergo multidisciplinary consultations before treatment. For stage III patients, TKIs were selected after individualized discussions to identify the most appropriate treatment option (for patients who disagreed with or were unsuitable for other standard treatment methods). Patients were treated with EGFR tyrosine kinase inhibitors (TKIs) as a first-line therapy, which included: Erlotinib 150mg, Gefitinib 250mg, Afatinib (40mg, 30mg, or 20mg), or Osimertinib (80mg). Patients were evaluated every two months for their treatment response and disease progression. If disease progression was observed, the patient was transitioned to a treatment plan in accordance with established guidelines.

Study Variables

The outcome variable was progression-free survival, defined as the period from treatment to either disease progression or death from any cause. Overall survival was calculated from the start of treatment until death from any cause.

Independent variables include

Age group (< 60 or > 60), Sex (Male or Female), Histopathology (AdenoCarcinoma or Other), PS ECOG (0-1 or 2-4), Stage (III or IV), Brain Metastases (Yes or No), Malignant Pleural Effusion (Yes or No), EGFR TKIs (Erlotinib, Gefitinib, Afatinib, or Osimertinib).

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation (SD) for data that follows a normal distribution, or as median with interquartile range (IQR) for data that does not follow a normal distribution. Qualitative variables are reported as frequencies and percentages (%).

Use the Kruskal-Wallis H-test to compare differences in quantitative variables with non-normal distributions between TKI drug groups. Compare differences between qualitative variables using the chi-square or Fisher's exact test.

Survival time (PFS and OS) was estimated using the Kaplan-Meier method and compared using the Log-Rank test. The association with various factors was evaluated using Cox regression. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). All analyses were performed using IBM SPSS 25.0. A p-value < 0.05 was considered statistically significant.

Results

The results of the study are presented in the tables and figures below. The patient groups were relatively homogeneous, except for gender differences. In addition, there was a trend toward a higher rate of brain metastases in the Osimertinib group (Table 1).

The median progression-free survival was 14.1 months (Figure 1A). The median overall survival was 24.9 months (Figure 1B). The median PFS of patients who received Erlotinib, Gefitinib, Afatinib, and Osimertinib was 11.2 months vs. 12.3 months vs. 16.8 months and 22.1 months, p = 0.003 (Figure 2A). The median OS of patients who received Erlotinib, Gefitinib, Afatinib, and Osimertinib was 17.6 months vs. 21.0 months vs. 30.4 months, and 41.6 months, p = 0.002 (Figure 2B).

In the entire population, PFS and OS were associated with EGFR TKIs (PFS: HR = 0.37, 95% CI:0.21-0.63 and OS: HR = 0.31, 95% CI: 0.15-0.63), MPE (PFS: HR = 0.62, 95% CI: 0.43-0.90 and OS: HR = 0.55, 95% CI: 0.38-0.81). PFS was associated with BM (HR = 0.58, 95% CI: 0.40-0.85) (Table 2A). To directly compare the two most effective agents from different generations, we performed an additional multivariate analysis with Afatinib as the reference group. Using the same model on the entire cohort (N=263), osimertinib remained associated with significantly better PFS (HR = 0.48, 95% CI: 0.25–0.94, p = 0.033) and OS (HR = 0.41, 95% CI: 0.18–0.97, p = 0.042) compared to afatinib specifically.

In the subgroup of patients with brain metastases, the point estimates favored osimertinib for both PFS (HR = 0.69) and OS (HR = 0.39); however, these associations did not reach statistical significance (p = 0.336 and p = 0.086, respectively), likely due to the limited sample size (n = 65) (Table 2B).

In patients with malignant pleural effusion, PFS was associated with brain metastases (HR = 0.53, 95% CI: 0.29-0.97), and the EGFR TKIs (HR = 0.40, 95% CI:

Table 1. Characteristics of Patients Participating in the Study

Variable	Total (n = 263)	Erlotinib (n = 63)	Gefitinib (n = 125)	Afatinib (n = 44)	Osimertinib (n = 31)	p- value
Age (years)						
Median (IQR)	69.0 (12)	70.0 (12)	69.0 (13)	69.0 (14)	68 (14)	0.796
Age group (years)						
< 60	41 (15.6)	10 (15.9)	21 (16.8)	6 (13.6)	4 (12.9)	0.93
> 60	222 (84.4)	53 (84.1)	104 (83.2)	38 (86.4)	27 (87.1)	
Sex (n, %)						
Male	113 (43.0)	26 (41.3)	44 (35.2)	31 (70.5)	12 (38.7)	0.001
Female	150 (57.0)	37 (58.7)	81 (64.8)	13 (29.5)	19 (61.3)	
PS (n, %)						
0-1	203 (77.2)	46 (73.0)	98 (78.4)	36 (81.8)	23 (74.2)	0.7
2-4	60 (22.8)	17 (27.0)	27 (21.6)	8 (18.2)	8 (25.8)	
Stage (n, %)						
III	30 (11.4)	8 (12.7)	14 (11.2)	5 (11.4)	3 (9.7)	0.98
IV	233 (88.6)	55 (87.3)	111 (88.8)	39 (88.6)	28 (90.3)	
BM (n, %)						
Yes	65 (24.7)	14 (22.2)	28 (22.4)	10 (22.7)	13 (41.9)	0.13
No	198 (75.3)	49 (77.8)	97 (77.6)	34 (77.3)	18 (58.1)	
MPE (n, %)						
Yes	109 (41.1)	23 (36.5)	58 (46.4)	15 (34.1)	13 (41.9)	0.41
No	154 (58.6)	40 (63.5)	67 (53.6)	29 (65.9)	18 (58.1)	
Histopathology						
Adenocarcinoma	253 (96.2)	60 (95.2)	121 (96.8)	42 (95.5)	30 (96.8)	0.89
Other	10 (3.8)	3 (4.8)	4 (3.2)	2 (4.5)	1 (3.2)	

BM, Brain Metastases; MPE, Malignant Pleural Effusion; IQR, Interquartile Range

Table 2. Association of Progression-free survival and Overall survival with factors: Cox regression analysis. 2A. The entire population.

Variable (N = 263)	PFS HR (CI 95%)	p	OS HR (CI 95%)	p
Age group (years)				
< 60	1	0.548	1	0.688
> 60	0.87 (0.57-1.35)		1.10 (0.68-1.79)	
Sex				
Male	1	0.713	1	0.185
Female	0.94 (0.67-1.31)		0.79 (0.55-1.12)	
PS ECOG				
0-1	1	0.118	1	0.123
2-4.	1.35 (0.93-1.96)		1.36 (0.92-2.03)	
Stage				
III	1	0.931	1	0.362
IV	0.98 (0.57-1.68)		0.77 (0.44-1.35)	
BM				
Yes	1	0.004	1	0.13
No	0.58 (0.40-0.85)		0.72 (0.48-1.10)	
MPE				
Yes	1	0.011	1	0.002
No	0.62 (0.43-0.90)		0.55 (0.38-0.81)	
EGFR TKIs				
1st – 2nd TKIs	1		1	0.001
Osimertinib	0.37 (0.21-0.63)	< 0.001	0.31 (0.15-0.63)	

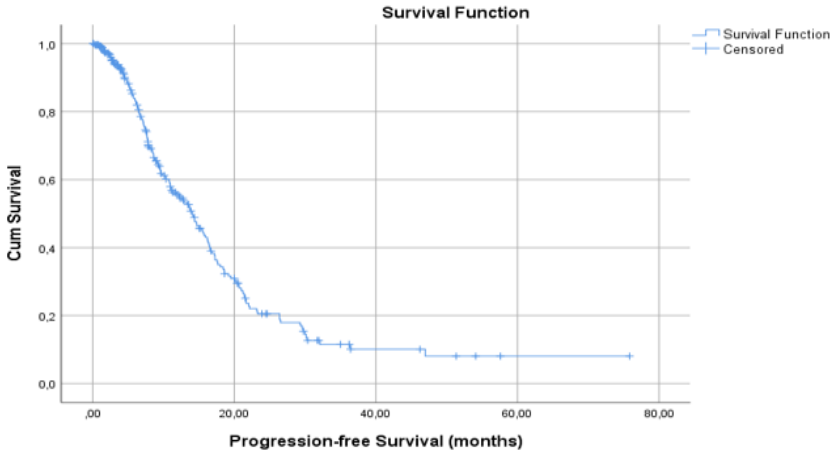
Note. BM, Brain Metastases; MPE, Malignant Pleural Effusion; EGFR TKIs, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor; HR, Hazard Ratio; PS, Performance status; PFS, Progression – free Survival; OS, Overall Survival.

0.16-0.95). OS was associated with EGFR TKIs (HR = 0.31, 95% CI: 0.11-0.87) (Table 2C). Treatment with afatinib was not associated with a statistically significant improvement in survival outcomes compared to erlotinib and gefitinib (PFS: HR = 0.70; 95% CI: 0.43–1.13, p = 0.143; OS: HR = 0.71; 95% CI: 0.42–1.19, p = 0.199) (Table 3).

Discussion

In Vietnam, there is limited data on the effectiveness of treatments for patients with non-small cell lung cancer who have EGFR mutations. Most studies have focused on the benefits of first-line targeted therapies in patients with both the EGFR L858R mutation in exon 21 and exon 19 deletions [8–10]. In the real-world context of Vietnam, treatment selection is influenced by multiple factors,

1A. Progression-free Survival



1B. Overall Survival

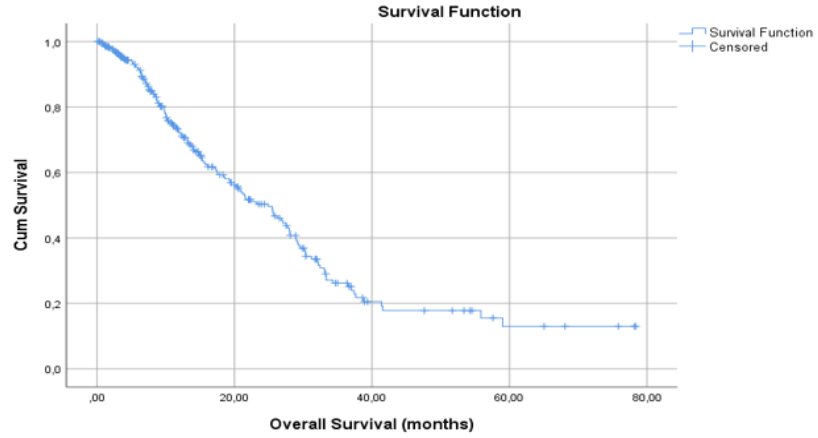


Figure 1. Progression-Free Survival and Overall Survival: Kaplan-Meier Analysis.

Table 2. Association of Progression-free survival and Overall survival with factors: Cox regression analysis. 2B. In patients with brain metastases

Variable	PFS		OS	
(N = 65)	HR (CI 95%)	p	HR (CI 95%)	p
Age group (years)				
< 60	1	0.36	1	0.32
> 60	1.49 (0.63-3.52)		1.74 (0.58-5.17)	
Sex				
Male	1	0.999	1	0.909
Female	1.00 (0.51-1.96)		1.05 (0.49-2.24)	
PS ECOG				
0-1	1	0.77	1	0.62
2-4.	1.11 (0.55-2.24)		1.20 (0.56-2.66)	
MPE				
Yes	1	0.257	1	0.173
No	0.67 (0.34-1.33)		0.60 (0.28-1.25)	
EGFR TKIs				
1st – 2nd TKIs	1		1	0.086
Osimertinib	0.69 (0.32-1.47)	0.336	0.39 (0.13 -1.14)	

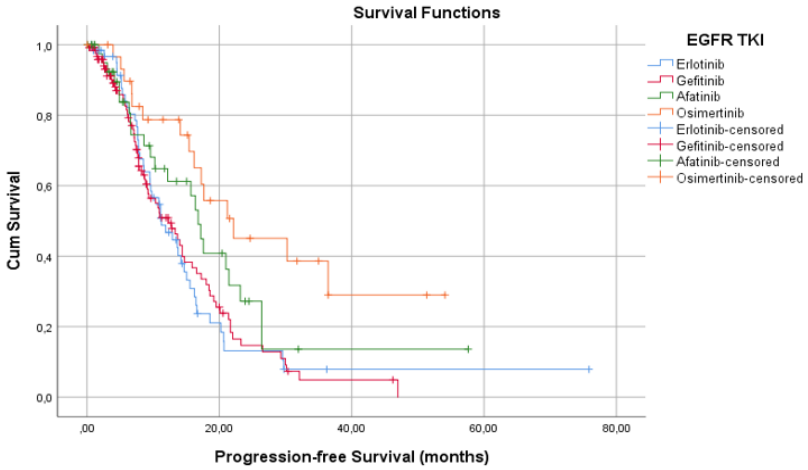
Note: MPE, Malignant Pleural Effusion; EGFR TKIs, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor; HR, Hazard Ratio; PFS, Progression – free Survival; OS, Overall Survival; PS, Performance status

Table 2. Association of Progression-free survival and Overall survival with factors: Cox regression analysis. 2C. In patients with malignant pleural effusion

Variable	PFS		OS	
(N = 65)	HR (CI 95%)	p	HR (CI 95%)	p
Age group (years)				
< 60	1	0.386	1	0.43
> 60	0.74 (0.38-1.45)		0.75 (0.39-1.46)	
Sex				
Male	1	0.198	1	0.091
Female	0.70 (0.41-1.20)		0.62 (0.36-1.08)	
PS ECOG				
0-1	1	0.513	1	0.312
2-4.	1.21 (0.69-2.13)		1.34 (0.76-2.35)	
BM				
Yes	1	0.04	1	0.324
No	0.53 (0.29-0.97)		0.72 (0.38-1.38)	
EGFR TKIs				
1st – 2nd TKIs	1		1	0.027
Osimertinib	0.40 (0.16-0.95)	0.04	0.31 (0.11-0.87)	

BM, Brain metastases; EGFR TKIs, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor; HR, Hazard Ratio; PFS, Progression – free Survival; OS, Overall Survival; PS, Performance status.

2A. Progression-free Survival



2B. Overall Survival

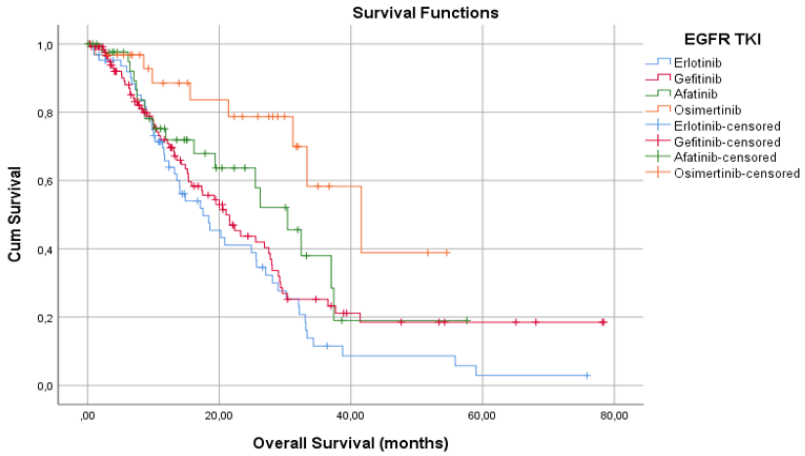


Figure 2. Progression-Free Survival and Overall Survival in the EGFR TKIs Group: Kaplan-Meier analysis, Log-rank test.

Table 3. Multivariate Cox Analysis of PFS and OS in Patients Treated with 1st - and 2nd -Generation EGFR TKIs.

Variable (N = 232)	PFS		OS	
	HR (CI 95%)	p	HR (CI 95%)	p
Age group (years)				
< 60	1	0.31	1	0.636
> 60	0.79 (0.50-1.24)		1.13 (0.68-1.86)	
Sex				
Male	1	0.441	1	0.286
Female	0.86 (0.60-1.25)		0.81 (0.56-1.19)	
PS ECOG				
0-1	1	0.222	1	0.555
2-4.	1.29 (0.86-1.94)		1.14 (0.74-1.75)	
Stage				
III	1	0.776	1	0.544
IV	1.08 (0.62-1.90)		0.84 (0.47-1.49)	
BM				
Yes	1	0.08	1	0.236
No	0.69 (0.46-1.05)		0.77 (0.50-1.19)	
MPE				
Yes	1	0.03	1	0.008
No	0.66 (0.45-0.96)		0.59 (0.40-0.87)	
EGFR TKIs				
Erlotinib & Gefitinib	1		1	
Afatinib	0.70 (0.43-1.13)	0.143	0.71 (0.42-1.19)	0.199

BM, Brain metastases; EGFR TKIs, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor; HR, Hazard Ratio; PFS, Progression – free Survival; OS, Overall Survival; PS, Performance status.

with treatment cost and insurance coverage playing a particularly significant role. First- and second-generation EGFR TKIs are partially reimbursed by national health insurance, whereas osimertinib is not covered. In addition, combination regimens (Osimertinib plus platinum-pemetrexed) have not yet been approved for routine clinical use. Therefore, the choice of treatment modalities in clinical practice also has certain limitations.

Our study focused on patients with EGFR L858R exon 21 mutations. We recorded progression-free survival and overall survival of 14.1 months and 24.9 months, respectively. These results are quite promising in the context of single-targeted agents. On the other hand, univariate and multivariate analyses showed that the survival benefits (PFS and OS) differed between agents, with osimertinib strongly favored. However, Afatinib did not demonstrate survival benefits when compared to first-generation TKIs.

The efficacy of osimertinib compared with first-generation EGFR TKIs in the L858R subgroup was also demonstrated in the FLAURA clinical trial [11]. Several recent studies have shown no difference in the efficacy of Afatinib and Osimertinib in patients with metastatic non-small cell lung cancer with EGFR exon 19 and L858R exon 21 mutations [12–14]. Even in the subgroup of patients with the L858R mutation without brain metastases, the survival benefit was superior with Afatinib compared with Osimertinib ($p < 0.001$) [15]. However, this study demonstrated the superior benefit of Osimertinib compared with Afatinib in PFS (HR = 0.48, 95% CI: 0.25–0.94, p = 0.033) and OS (HR = 0.41, 95% CI: 0.18–0.97, p = 0.042). This difference may be due to variations in the patient subgroups treated. Specifically in our study, the group of patients treated with osimertinib had a higher rate of brain metastasis compared to other groups. This further confirms the superiority of osimertinib over 1st and 2nd-generation EGFR TKIs.

In Asian patients with the EGFR L858R mutation, EGFR TKIs and combination therapies did not improve overall survival compared to chemotherapy. However, Pemetrexed combined with Gefitinib, Dacomitinib, Osimertinib, and Erlotinib plus Bevacizumab increased progression-free survival [16]. Additionally, combining anti-angiogenic drugs (VEGF inhibitors) is shown to be more effective than single-agent therapy [6, 17, 18]. Despite these clinical findings, health insurance reimbursement policies limit patient access to combination treatments. Consequently, standard EGFR TKI therapy remains most widely used.

Afatinib was not associated with a statistically significant improvement in survival outcomes compared to erlotinib and gefitinib (PFS: HR = 0.70, 95% CI: 0.43–1.13, p = 0.143; OS: HR = 0.71, 95% CI: 0.42–1.19, p = 0.199) (Table 3). This finding aligns with the results of the Lux-Lung 7 study, which compared the efficacy of Afatinib and Gefitinib in patients harboring the L858R mutation in exon 21 [16]. In another retrospective study (n = 237), the prevalence of EGFR L858R mutations, other uncommon mutations, and exon 19 deletions was 35.4%, 9.7%, and 54.9%, respectively. This study showed that Afatinib had a significantly better PFS (p=0.042) and a trend toward better OS (p=0.069) than first-generation EGFR TKIs in the subgroup of patients with EGFR L858R mutations and uncommon mutations [17]. The advantage of Afatinib over 1st EGFR TKIs may be due to its effect on the group of patients with uncommon gene mutations.

In patients with brain metastases, Osimertinib also had a better overall survival, although the difference was not statistically significant (Table 2B). This may be due to the insufficient sample size, especially in the Osimertinib-treated group. Data showed that progression-free survival and overall survival in patients with brain metastases with EGFR L858R were quite low (10.0 months and 17.4 months) [18]. Previous data also showed that in patients with EGFR L858R mutation and brain metastases, third-generation EGFR TKIs were more effective than first- and second-generation EGFR TKIs, including cases with TP53. In particular, the combination chemotherapy regimen with third-generation EGFR TKIs was more effective than all other methods [19]. Additionally, in an analysis of patients with EGFR-positive brain metastases with non-small cell lung cancer, afatinib had a lower cumulative incidence of central nervous system dysfunction than gefitinib and erlotinib after adjusting for both mutation type and pre-existing central nervous system metastases [20]. Osimertinib's superior ability to cross the blood-brain barrier is also a basis for clinicians to guide treatment selection in this particular patient group [21].

In the group of patients with malignant pleural effusion, Osimertinib was effective in both PFS and OS compared with first-generation EGFR TKIs (Table 2C). Previous studies showed that PFS and OS in patients with malignant pleural effusion with EGFR L858R exon 21 mutation were lower than those with Del exon 19 mutation (7.1 months vs. 9.4 months and 13.8 months vs. 16.8 months, $p < 0.05$) [22]. In addition, malignant pleural effusion is a prognostic factor that negatively affects survival time when treated with first-generation EGFR TKIs, but it is not affected when treated with Osimertinib [23, 24]. These data further confirm the evidence of the efficacy of Osimertinib in the patient population with pleural fluid metastases.

This study has several limitations that should be acknowledged. First, its retrospective design may introduce inherent biases. Second, the relatively small sample size, particularly for the Osimertinib group, limits the statistical power for subgroup analyses. Furthermore, several important confounding factors, such as smoking status, comorbidities, and co-mutation profiles, could not be fully evaluated due to the retrospective data collection. Most importantly, data on adverse events were not comprehensively or systematically recorded, precluding a formal safety analysis. Despite these limitations, our findings provide valuable real-world insights to guide treatment decisions for NSCLC patients with EGFR L858R mutations, especially in the presence of brain metastases or malignant pleural effusions. Beyond its immediate implications for Vietnam, this study offers valuable insights for other low- and middle-income countries (LMICs) facing similar healthcare resource constraints. In many LMICs, access to newer-generation TKIs like osimertinib is often limited by high costs and restricted health insurance coverage. Therefore, real-world evidence from settings like ours is crucial for informing clinical practice in these contexts. Our findings, particularly the demonstrated superiority of osimertinib in high-risk subgroups such as patients with brain metastases or malignant pleural effusion, can help clinicians in LMICs prioritize this effective, albeit less

accessible, therapy for the patients most likely to derive substantial benefit. This study underscores the need for further pharmacoeconomic evaluations within LMICs to support evidence-based policymaking and optimize the allocation of limited healthcare resources.

Author Contribution Statement

PVH, DHN, NKT, NVL developed the idea and study design, analyzed and interpreted the data, and wrote the article. PTH, VTHA, PTT, VTMH, LTHY, NTTM, LVT, TTTH, TTT, and TKH contributed to data collection. All authors read and approved the final article.

Acknowledgements

This article represents the author's personal views and does not represent the views of other organizations with which the authors are affiliated.

Ethical approval

The Ethics Committee of Nghe An Oncology Hospital approved the study proposal. In addition, patient records were anonymized and de-identified before undergoing analysis. Informed consent was waived due to the retrospective nature of this study

Availability of data and material

We agree to publish the research article according to the guidelines.

Data Availability Statement

Data will be provided upon reasonable request.

Funding Sources

This study was not supported by any sponsor or funder

Conflict of Interest

The authors have no conflicts of interest to declare.

Abbreviations

AJCC: American Joint Committee on Cancer
BM: Brain Metastases
CI: Confidence Interval
EGFR TKI: Epidermal Growth Factor Receptor Tyrosine Kinase inhibitors
HR: Hazard Ratio
MPE: Malignant Pleural Effusion
NGS: Next Generation Sequencing.
SD: Standard Deviation
Real-time PCR: Real-time Polymerase Chain Reaction.
PFS: Progression-free survival
OS: Overall survival
IQR: Interquartile Range

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