ORIGINAL ARTICLE

Clinical Treatment Outcomes of Erlotinib in Metastatic Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Real-World Data Study

Chalita Lagampan, MD[1]

[1] Division of Medical Oncology, Department of Internal Medicine, Chonburi Hospital, Chonburi, Thailand

Background: Patients with non-small cell lung cancer (NSCLC) harboring uncommon epidermal growth factor receptor (EGFR) mutations often exhibit variable responses to EGFR tyrosine kinase inhibitors (TKIs).

Objective: To evaluate the clinical outcomes of first-line erlotinib in patients with advanced NSCLC harboring uncommon EGFR mutations, compared to those with common mutations.

Materials and Methods: The present study was a retrospective study conducted on 193 patients with advanced NSCLC and documented EGFR mutations, treated with erlotinib at Chonburi Hospital, Thailand, between January 1, 2020, and December 31, 2023. The authors collected data on patient demographics, mutation types, treatment regimens, progression-free survival (PFS), overall survival (OS), and physician-assessed objective response rates.

Results: Patients with uncommon EGFR mutations, which include 10.3%, had significantly shorter median OS of 7.6 months (95% CI 3.2 to 12.0) and PFS of 5.7 months (95% CI 0.0 to 11.4) compared to those with common EGFR mutations with a median OS of 19.5 months (95% CI 15.8 to 23.2) and a median PFS of 11.0 months (95% CI 9.2 to 12.7). The objective response rate to erlotinib was lower in patients with uncommon mutations (33.3% had partial responses) compared to those with common mutations (78.1% for exon 19 deletion and 82.4% for L858R). Multivariate analysis identified ECOG performance status as a significant prognostic factor for survival in patients with uncommon EGFR mutations.

Conclusion: Patients with advanced NSCLC harboring uncommon EGFR mutations exhibit poorer survival outcomes with first-line erlotinib treatment compared to those with common mutations. Alternative treatment strategies and personalized approaches are warranted for these patients.

Keywords: Uncommon EGFR mutations; Non-small cell lung cancer; Compound EGFR mutations; Erlotinib; Personalized treatment strategies

Received 16 May 2025 | Revised 17 January 2026 | Accepted 19 January 2026

J Med Assoc Thai 2026;109(3):178-86

Website: http://www.jmatonline.com

Mutations in the epidermal growth factor receptor (EGFR) gene are critical oncogenic drivers in non-small cell lung cancer (NSCLC). Approximately 50% of Asian and 10% to 20% of Caucasian NSCLC patients exhibit these mutations, primarily occurring in exons 18 to 21, which include the tyrosine kinase binding domain of EGFR. The most prevalent mutations, exon 19 deletions (E19del) and the L858R point mutation in exon 21, collectively known as "common EGFR mutations", account for 42% to 50% and 32.84% to 42% of EGFR mutations, respectively. These common mutations are associated with high sensitivity to EGFR tyrosine kinase inhibitors (TKIs) and represent approximately 80% to 90% of EGFR gene alterations[1].

In contrast, uncommon EGFR mutations comprise 6.1% to 23% of EGFR mutation-positive NSCLC cases. These mutations, including de novo T790M mutations, exon 20 insertions, and major uncommon mutations such as G719X at 2% to 6%, L861Q at 1.3% to 3.2%, and S768I at 1.3% to 3%[2], exhibit high heterogeneity. Additional rare mutations, like E709X, with less than 0.5%, also contribute to the diverse genetic landscape. Exon 20 insertions and T790M mutations typically show resistance to EGFR-TKI therapy, while responses to other uncommon mutations vary[3].

The development of EGFR-TKIs has transformed the treatment landscape for EGFR mutation-positive

Correspondence to:

Lagampan C.

Division of Medical Oncology, Department of Internal Medicine, Chonburi Hospital, Chonburi 20000, Thailand.

Phone: +66-89-2018454

Email: zenith_nna@hotmail.com

How to cite this article:

Lagampan C. Clinical Treatment Outcomes of Erlotinib in Metastatic Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Real-World Data Study. J Med Assoc Thai 2026;109:178-86.

DOI: 10.35755/jmedassocthai.2026.3.178-186-03126

NSCLC. These inhibitors are categorized into three generations: first-generation (1G) TKIs like gefitinib and erlotinib, which reversibly inhibit EGFR signaling; second-generation (2G) TKIs like afatinib and dacomitinib, which irreversibly block signaling from all ErbB family receptor dimers; and third-generation (3G) TKIs like osimertinib, which target EGFR mutations and T790M resistance mutations specifically. These treatments have shown significant survival benefits over platinum-based chemotherapy and are approved for first-line treatment in advanced EGFR-mutant NSCLC. Notably, studies such as LUX-Lung 2, 3, and 6 for afatinib and the FLAURA trial for osimertinib have demonstrated improved survival outcomes, with the FLAURA trial reporting an overall survival (OS) of 38.6 months with frontline osimertinib compared to 31.8 months with erlotinib or gefitinib[4]. Sequential treatment strategies, exemplified by the GioTag study, revealed a median OS of 41.3 months with sequential afatinib and osimertinib, increasing to 45.7 months in patients with E19del mutations[5].

However, the efficacy of TKIs in treating uncommon EGFR mutations is less understood, based on retrospective studies and case reports[6]. First-generation TKIs have shown modest effectiveness, with a reported median progression-free survival (PFS) of approximately 6.2 months for mutations like G719X, L861Q, and S768I[7]. Second-generation TKIs have demonstrated improved outcomes in these mutations, suggesting higher efficacy compared to first-generation agents[8]. Data on third-generation TKIs for uncommon mutations are limited, focusing mostly on common mutations or T790M-positive cases[9]. The impact of compound mutations, involving more than one EGFR mutation within the same tumor, on TKI sensitivity and resistance remains poorly understood due to their heterogeneity and the variability in molecular testing methods[10].

The present study aimed to present real-world data on practice patterns and treatment outcomes, comparing patients with common and uncommon EGFR mutation-positive NSCLC, focusing on PFS, OS, and physician-assessed objective response rates.

Material and Methods

Patients

Between January 1, 2020, and December 31, 2023, patients diagnosed with histologically confirmed NSCLC harboring EGFR mutations were retrospectively screened at Chonburi Hospital, Thailand. The present study included treatment-naïve patients with recurrent or metastatic NSCLC who harbored either common or uncommon EGFR mutations and who had received erlotinib. Given that uncommon EGFR mutations represent a small subset of the NSCLC population, all consecutive patients diagnosed with metastatic NSCLC and treated with erlotinib at Chonburi Hospital between January 2020 and December 2023 were screened. All individuals meeting the predefined inclusion criteria were enrolled to ensure the maximum possible sample size for this real-world analysis. Patients were excluded if their treatment was discontinued for reasons not related to disease progression, such as poor performance status, infections, or transfer to other hospitals. A retrospective review of electronic medical records captured demographic and clinical variables, including age, sex, comorbidities, smoking history, EGFR mutation type, TNM stage based on the Eighth edition, treatment regimens, PFS, OS, and physician-assessed objective response rate. The present study received approval from the Institutional Review Board of Chonburi Hospital, research code 2/67/S/h3, and exempted from obtaining informed consent due to the retrospective nature of the study design.

Histology and mutation analysis of EGFR

Tumor tissues were collected through CT-guided needle biopsy, bronchoscopic biopsy, and surgical resection. DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. EGFR mutation analysis varied by timeframe and facility. Between 2020 and 2022, it was performed by N Health Bio Molecular Laboratories (Thailand) Co., Ltd. using the Food and Drug Administration (FDA)-approved cobas EGFR Mutation Test v2 (Roche Molecular Systems, Inc.). Between 2022 and 2023, testing was conducted by Sanomics (Thailand) Limited using real-time PCR technology.

Evaluation of efficacy

Erlotinib was administered at a dose of 150 mg orally once daily until disease progression or unacceptable toxicity occurred. Patients were initially advised to visit the clinic within two to three weeks of starting treatment, with follow-ups scheduled every four to eight weeks, assuming no severe adverse events were observed. Chest computed tomography scans were conducted every one to three months to assess treatment response. The objective response rate was determined based on the best response, categorized as complete response (CR), partial

Table 1. Baseline characteristics of patients

Patient characteristics	Total (n=193)	E19del (n=105)	L858R (n=68)	Uncommon (n=12)	Compound (n=8)	p-value
Age (years); mean±SD	64.4±10.8	62.2±10.7	67.4±10.7	63.1±8.2	69.9±10.2	0.007
Sex: male; n (%)	69 (35.8)	35 (33.3)	23 (33.8)	5 (41.7)	6 (75)	0.115
ECOG performance status; n (%)						0.503
0	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	
1	130 (67.4)	71 (67.6)	41 (63.2)	8 (66.7)	8 (100)	
2	62 (32.1)	33 (31.4)	21 (36.8)	4 (33.3)	0 (0)	
Smoker; n (%)	51 (26.4)	27 (25.7)	17 (25.0)	4 (33.3)	3 (37.5)	0.826
History of curative thoracic surgery; n (%)	17 (8.8)	9 (8.6)	7 (10.3)	1 (8.3)	0 (0)	0.808
History of previous chemotherapy; n (%)	6 (3.1)	4 (3.8)	1 (1.5)	1 (8.3)	0 (0)	0.548
History of radiation; n (%)	45 (23.3)	27 (25.7)	15 (22.1)	3 (25.0)	0 (0)	0.415
Histology; n (%)						0.706
Adenocarcinoma	189 (98.4)	104 (99.0)	66 (97.1)	12 (100)	7 (87)	
Squamous cell carcinoma	3 (1.6)	1 (1.0)	2 (2.9)	0 (0.0)	0 (0)	
Mix adenosquamous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	
Brain metastasis; n (%)	43 (22.3)	26 (24.8)	15 (22.1)	2 (16.7)	0 (0)	0.409
Received subsequent treatment; n (%)	91(47.1%)	53(50.4%)	33(48.5%)	3 (25.0%)	2 (25.0%)	0.043

E19del=exon 19 deletion; ECOG=Eastern Cooperative Oncology Group; SD=standard deviation

response (PR), stable disease (SD), or progressive disease (PD). Specifically, CR was defined as the total disappearance of all detectable lesions. PR was characterized by a significant reduction of 30% or more in tumor burden. SD indicated a lack of significant change in tumor size that did not meet the criteria for response or progression. PD was defined as a significant increase in tumor size of 20% or more, the emergence of new metastatic lesions, or clear clinical evidence of disease worsening. These categories were evaluated by experienced oncologists through a systematic review of radiological images and clinical findings to ensure a consistent assessment across the cohort. PFS was defined as the time from initiation of EGFR TKI therapy to the first documented disease progression or death from any cause, whichever occurred first. OS was defined as the time from initiation of EGFR TKI therapy to death from any cause. The data cutoff date was December 31, 2024.

Statistical analysis

Categorical variables were compared using Pearson's chi-square test, while continuous variables were analyzed with a one-way analysis of variance (ANOVA). PFS and OS were expressed as median values with two-sided 95% confidence intervals (CIs). Differences in PFS and OS between the common and uncommon EGFR mutation groups were evaluated using the log-rank test and visualized with Kaplan-Meier curves. Multivariate analyses for PFS and OS were conducted using Cox regression models. Statistical significance was defined as a two-sided p-value of less than 0.05. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristic

Between January 1, 2020, and December 31, 2023, 199 advanced and recurrent NSCLC patients were tested for EGFR mutations and treated with erlotinib. After excluding six cases for eligibility reasons, 193 patients with advanced lung adenocarcinoma were analyzed. The average age was 64.4 years (SD ±10.8), with a majority being female at 64.2% and never smoking at 73.5%. Most patients (67.9%) had the Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1. Mutation analysis showed that 54.4% had E19del, 35.2% had L858R, and 10.3% had uncommon mutations, including G719X, L861Q, and S781I. Compound mutations were found in 4.1% of the cohort. Table 1 and 2 categorized and detailed these mutations, illustrating the prevalence of common mutations at 89.6%, with less frequent, diverse uncommon mutations comprising 10.3% of the study population. Notably, regarding treatment adherence and safety, all patients in both groups received the full standard dose of erlotinib without any requirement for dose reduction or interruption due to serious adverse events.

Table 2. EGFR mutation subtypes

Mutation type	Exon	Number of patients	Percentage (%)	Total (n=193)
Common mutations				89.6
E19del	19	105	54.4	
L858R	21	68	35.2	
Uncommon mutations				10.3
G719X	18	7	3.6	
S768I	20	1	0.5	
Exon 20 insertion	20	1	0.5	
L861Q	21	3	1.6	
Compound mutations				4.1
G719X + S768I	-	4	2.1	
E19del + T790M	-	2	1.0	
L858R + T790M	-	1	0.5	
L858R + G719X	-	1	0.5	

E19del=exon 19 deletion

Clinical outcomes of erlotinib treatment

1) Survival outcomes:

At the time of data cutoff, the majority of the cohort had experienced a clinical event. Specifically, 170 patients (88.1%) reached the study endpoints of disease progression or death. Conversely, 23 patients (11.9%) remained alive and progression-free and were censored in the survival analysis. The overall median survival for the entire cohort was 17.1 months (95% CI 14.0 to 20.2). Survival outcomes varied significantly according to EGFR mutation status, as illustrated in Figure 1A. The 173 patients harboring common EGFR mutations exhibited a median OS of 19.5 months (95% CI 15.8 to 23.2). Conversely, the 20 patients with uncommon or compound EGFR mutations demonstrated a markedly reduced median OS of 7.6 months (95% CI 3.2 to 12.0, Log-rank p<0.001).

Analysis of PFS similarly demonstrated significant variation across mutation subtypes, as shown in Figure 1B. Among patients with common mutations, the median PFS was 11.0 months (95% CI 9.2 to 12.7). In contrast, patients with uncommon or compound mutations exhibited a significantly shorter median PFS of 7.1 months (95% CI 4.2 to 9.9, Log-rank p<0.001).

2) Physician-assessed objective response rate:

Objective response rates assessed by physicians revealed differing levels of PR and SD across mutation subtypes. For patients with E19del and L858R mutations, the rates of PR were 78.1% and 82.4%, respectively. In contrast, patients with uncommon mutations and compound mutations exhibited lower

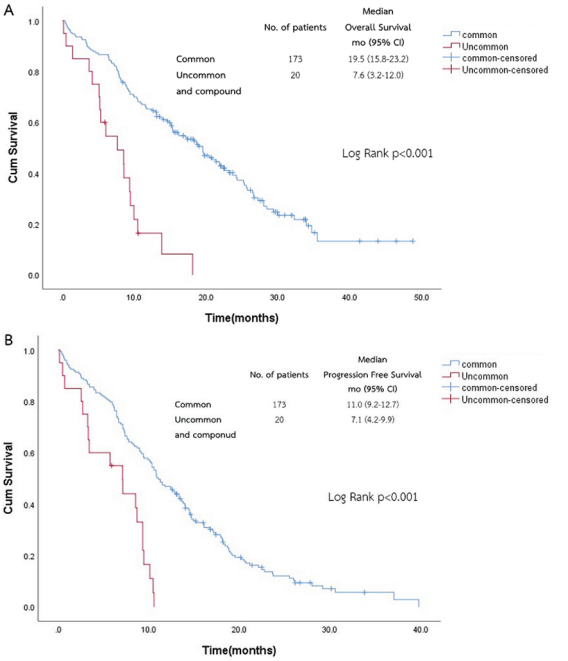

Figure 1. Kaplan-Meier analysis comparing common and uncommon EGFR mutations in NSCLC. (A) Overall survival, (B) Progression free survival.

Table 3. Physician-assessed objective response rate of erlotinib according to mutation type

Category	PR; n (%)	SD; n (%)	PD; n (%)	p-value
Total (n=193)	146 (75.6)	36 (18.7)	11 (5.7)	<0.003
E19del (n=105)	82 (78.1)	19 (18.1)	4 (3.8)	
L858R (n=68)	56 (82.4)	9 (13.2)	3 (4.4)	
Uncommon (n=12)	4 (33.3)	6 (50.0)	2 (16.7)	
Compound (n=8)	4 (50.0)	2 (25.0)	2 (25.0)	

PR=partial response; SD=stable disease; PD=progressive disease; E19del=exon 19 deletion

PR rates of 33.3% and 50%, respectively. Rates of SD followed a similar trend, with 18.1% for E19del, 13.2% for L858R, 50% for uncommon mutations, and 25% for compound mutations. These variations in response rates were statistically significant (p<0.03), detailed in Table 3.

Prognostic factors for common and uncommon EGFR Mutations treated with erlotinib

Multivariable Cox regression analysis (Table 4) identified ECOG PS 2, when compared to PS 0 to 1, as the strongest independent predictor of inferior outcomes in the uncommon mutation subgroup. This factor significantly worsened both PFS (adjusted HR 6.69, 95% CI 1.24 to 35.94, p=0.027) and OS (adjusted HR 19.77, 95% CI 2.52 to 154.87, p=0.004).

Table 4. Multivariate analyses for prognostic factors in patients with uncommon EGFR (including compound mutations) and common EGFR mutation treated with erlotinib as first-line therapy

Variable	PFS; adjusted HR (95% CI)		OS; adjusted HR (95% CI)	
	Uncommon EGFR mutations	Common EGFR mutations	Uncommon EGFR mutations	Common EGFR mutations
Age (<65 vs. ≥ 65 years)	0.55 (0.16 to 1.81)	0.81 (0.57 to 1.15)	0.40 (0.12 to 1.35)	1.03 (0.70 to 1.53)
p-value	0.324	0.249	0.141	0.865
Sex (male vs. female)	2.49 (0.58 to 10.75)	1.09 (0.70 to 1.68)	2.02 (0.45 to 9.06)	1.20 (0.74 to 1.92)
p-value	0.221	0.706	0.358	0.461
Smoking status (smoker vs. non-smoker)	0.16 (0.23 to 1.01)	1.34 (0.84 to 2.13)	0.32 (0.60 to 1.60)	1.41 (0.85 to 2.32)
p-value	0.051	0.213	0.165	0.181
ECOG PS (PS 2 vs. PS 0-1)	6.69 (1.24 to 35.94)	1.37 (0.18 to 10.48)	19.77 (2.52 to 154.87)	1.96 (0.25 to 15.22)
p-value	0.027	0.761	0.004	0.518
Brain metastasis (presence vs. absence)	5.42 (0.79 to 37.30)	1.11 (0.73 to 1.67)	6.59 (0.85 to 50.86)	1.26 (0.80 to 2.00)
p-value	0.086	0.627	0.070	0.314

PFS=progression-free survival; OS=overall survival; EGFR=epidermal growth factor receptor; ECOG PS=Eastern Cooperative Oncology Group performance status

Table 5. Subsequent treatment modalities and essential therapeutic agents administered following first-line erlotinib by EGFR mutation category

Mutation category	Total patients	Received 2nd line; n (%)	Osimertinib; n (%)	Platinum-based chemotherapy; n (%)	Others; n (%)
Common (E19del/L858R)	173	86 (49.7)	14 (16.3)	68 (79.1)	4 (4.6)
Uncommon (single)	12	3 (25.0)	0 (0.0)	3 (100)	0 (0.0)
Compound	8	2 (25.0)	0 (0.0)	2 (100)	0 (0.0)
Overall (n=193)	193	91 (47.1)	14 (15.4)	73 (80.2)	4 (4.4)

E19del=exon 19 deletion

In contrast, ECOG PS 2 did not reach statistical significance for patients with common mutations (PFS: p=0.761, OS: p=0.518).

Other clinical variables, including brain metastases at diagnosis, as presence versus absence, showed higher hazard ratios (HRs) in the uncommon group (OS: adjusted HR 6.59, 95% CI 0.85 to 50.86, p=0.165) compared to the common group (OS: adjusted HR 1.26, 95% CI 0.80 to 2.00, p=0.181), though these did not achieve independent statistical significance as their 95% CIs crossed 1.0. Similarly, age as younger than 65 versus 65 years and older, sex as male versus female, and smoking status as smoker versus non-smoker were not significant prognostic indicators across both subgroups, with all 95% CIs encompassing 1.0. Notably, smoking status in the uncommon group showed a trend toward significance for PFS (adjusted HR 0.16, 95% CI 0.23 to 1.01, p=0.051).

Clinical outcomes of the second line and beyond treatment

Among the 86 patients identified with common EGFR mutations of E19del and L858R, 21 (24.4%) underwent testing for the T790M mutation, with 16 (76.2%) testing positive. In contrast, of the five patients with either uncommon or compound EGFR mutations, only one (20%) was tested for T790M, and none were found to have the mutation. This discrepancy highlights the limitations imposed by the small sample size of patients with uncommon mutations.

Following erlotinib failure, 91 patients (47.1%) transitioned to second-line (2L) therapy. The distribution of essential subsequent treatments varied significantly by mutation subtype, as detailed in Table 5. Among patients with common mutations, approximately half were able to receive subsequent treatment (50.4% for E19del and 48.5% for L858R). Notably, osimertinib was administered exclusively to 14 patients (15.4%) within the common mutation group, following confirmed T790M resistance. For the majority of patients in the present group who did not receive osimertinib, platinum-based chemotherapy was the standard of care, primarily consisting of the Carboplatin plus Paclitaxel regimen. In contrast, patients with uncommon (12 patients) and compound mutations (8 patients) had limited

therapeutic sequences. Only 25% of patients in these subgroups were fit enough to initiate 2L therapy, and none received osimertinib. Their subsequent treatment consisted entirely of chemotherapy.

Regarding the overall chemotherapy landscape, while platinum-doublets (Carboplatin/Paclitaxel) dominated the 2L setting (80.2%), treatment for those progressing to further lines (3L to 7L) shifted toward single-agent or alternative regimens. This included Docetaxel as the predominant 3L therapy, while 4L and 5L lines consisted of Carboplatin/Etoposide and Carboplatin/Gemcitabine, respectively. These patterns reflect the real-world constraints and the limited window for targeted intervention in patients with non-classic EGFR mutations compared to those with common mutations.

Discussion

The present study evaluates the clinical outcomes of 193 NSCLC patients, situating the findings within the broad spectrum of global EGFR research. Consistent with established literature, the majority of mutations in the cohort were classic types, such as E19del and L858R, which remain the predominant variants worldwide[1,11]. However, the present study results underscore the profound clinical challenges posed by uncommon and compound mutations. While prior studies indicate that variants such as G719X, L861Q, and S768I occur in only 1% to 6% of cases[12], their high heterogeneity leads to highly variable and inferior treatment responses compared to common mutations[7,13-17].

In the present study cohort, the median OS for patients with common mutations was 19.5 months, whereas it dropped sharply to 6.0 months for uncommon and 7.6 months for compound mutations. Kaplan-Meier curves further revealed a rapid decline in survival probabilities for these non-classic subgroups within the first 10 months of treatment. Notably, the gap between median PFS and OS in these patients was remarkably narrow, a phenomenon reflecting the aggressive biological behavior of these variants and the rapid clinical deterioration following initial treatment failure. This grim prognosis is further exacerbated by the limited access to effective subsequent therapies in our resource-constrained setting, where only a minority of patients remained fit enough to receive 2L treatment after progressing on erlotinib.

Beyond first-generation TKIs, international clinical trials have explored the efficacy of subsequent-generation agents in non-classic EGFR subsets. The LUX-Lung 3 and LUX-Lung 6 trials, which were phase III randomized controlled trials evaluating afatinib versus chemotherapy, provided pooled post-hoc analyses focusing on patients with uncommon mutations (defined here as all mutations excluding E19del and L858R, such as G719X, L861Q, and S768I). These analyses suggested that afatinib possesses clinical activity against certain uncommon variants, showing more favorable outcomes compared to chemotherapy or first-generation TKIs in those specific subgroups[3,12,18-21]. Similarly, retrospective studies from Europe have reported the clinical activity of osimertinib in this population, particularly for G719X, L861Q, and S768I[12,22]. It is important to note that uncommon mutations, a heterogeneous group including both sensitizing and less-sensitive variants, are distinct from rare mutations, which typically refer to extremely low-frequency alterations (occurring in less than 1% of cases) or those with poorly characterized drug sensitivity. While the favorable PFS and response rates reported in these international trials and registries provide a benchmark for TKI activity, they cannot be directly compared with our findings due to significant differences in study designs, patient demographics, and lines of therapy. Nevertheless, these advancements highlight a disparity in care.

Multivariable Cox regression analysis for the entire cohort identified key prognostic indicators affecting survival. A poor ECOG PS (PS 2) was the strongest predictor of inferior outcomes, significantly worsening both PFS (HR 6.69) and OS (HR 19.77). Additionally, the presence of brain metastases was associated with shorter survival, particularly in the uncommon mutation group, a finding that underscores the limited CNS penetration of first-generation TKIs like erlotinib[6,23,24]. Crucially, these prognostic factors directly influenced the feasibility of subsequent treatments, which we identified as a major determinant of OS. Patients with better performance status and common mutations were significantly more likely to receive multiple lines of therapy, whereas those with uncommon mutations often experienced rapid clinical deterioration, precluding further active treatment[25-29]. While intensified regimens like the ABCP protocol in the IMpower150 study have shown promise after TKI failure[30], the majority of our patients received single-agent or platinum-based chemotherapy. The present study findings suggest that the inability to transition to subsequent therapy, often due to the aggressive nature of uncommon variants and poor baseline PS,

accounts for the narrow gap between PFS and OS observed in these subgroups.

Regarding resistance mechanisms, acquired T790M mutations typically emerge in approximately 60% of patients after 9 to 13 months of first-line therapy[31]. In the present study, however, only 24% of patients underwent T790M testing upon progression. This low testing rate reflects the reimbursement landscape in Thailand, where access to Osimertinib, the standard of care for T790M-positive cases, is often restricted by cost or specific eligibility criteria. While we observed a higher prevalence of T790M in common mutations, at 76.2%, compared to uncommon variants, the small number of patients tested in the uncommon group remains a significant limitation, preventing definitive conclusions regarding mutation-specific resistance patterns.

The present analysis suggests that the prognosis of compound mutations is determined by a complex biological interplay between individual mutation components. For instance, patterns involving a 'common' sensitizing mutation such as E19del or L858R, may partially preserve TKI responsiveness, yet the clinical outcome is shaped by the specific molecular synergy of the co-mutation, which can alter drug-binding affinity or activate bypass signaling pathways. This underscores that managing these patients requires more than simple categorization. It necessitates a profound understanding of how specific co-mutations modulate the therapeutic threshold of EGFR-TKIs.

Beyond these biological complexities, the present findings highlight a critical gap in health equity and drug reimbursement policy in Thailand. The markedly inferior outcomes observed in patients with uncommon and compound mutations, compared to those with common mutations, underscore the clinical consequences of restricted access to newer-generation TKIs. While international guidelines recommend second- or third-generation TKIs for these subsets, erlotinib remains the primary option under the National List of Essential Medicines (NLEM) and major healthcare schemes such as the universal coverage scheme, social security scheme, and civil servant medical benefit scheme. The present study data demonstrate that relying on first-generation TKIs for these high-risk variants often results in rapid progression and limited subsequent treatment opportunities. These results advocate for a policy reassessment to include targeted therapies for uncommon EGFR subsets within the national framework, ensuring that treatment selection is driven by clinical evidence rather than economic constraints.

Limitation

Limitations of the present study should be acknowledged. First, its retrospective, single-center design and small cohort of patients with uncommon mutations may limit the generalizability of the findings and the statistical power for subgroup analyses. Second, the reliance on electronic medical records risks incomplete data and potential selection bias, as patients who discontinued treatment for reasons other than disease progression were excluded. Additionally, although baseline performance status was well-balanced, detailed information on specific comorbidities was not systematically analyzed, which may leave residual confounding factors unaddressed. Third, heterogeneity in EGFR testing methods—shifting between Real-time PCR and cobas platforms over time—and the absence of a central pathology review may have introduced assay-related variability.

Furthermore, clinical outcomes were based on physician-assessed responses without strict RECIST 1.1 confirmation, introducing potential subjectivity. The variability in follow-up intervals (4 to 8 weeks) and imaging frequency (1 to 3 months), inherent in real-world clinical practice, may have influenced the precise timing of progression assessment. Lastly, although the authors had addressed the time-origin mismatch by measuring both PFS and OS from the initiation of erlotinib, the disparate follow-up durations due to the fixed data cutoff and the exemption from informed consent, which limited the verification of clinical nuances, remain recognized constraints of this real-world evidence.

Conclusion

The present real-world study reveals that patients with uncommon and compound EGFR mutations exhibit a poorer response to erlotinib compared to those with common mutations. Clinically, this suggests the need for alternative first-line treatments, such as afatinib or Osimertinib, and closer monitoring for patients with brain metastases or poor performance status.

What is already known about this topic?

Erlotinib has shown effectiveness in treating NSCLC patients with common EGFR mutations of E19del and L858R, while its efficacy in patients with uncommon or compound EGFR mutations remains unclear, especially in resource-limited settings like Thailand, where access to newer TKIs is restricted.

Understanding the real-world outcomes of erlotinib in this population could guide more effective treatment strategies.

What does this study add?

This study demonstrates that NSCLC patients with uncommon or compound EGFR mutations have significantly worse clinical outcomes with first-line erlotinib compared to those with common mutations. The findings highlight the urgent need for alternative first-line therapies and improved access to next-generation TKIs in Thailand to improve patient survival.

Acknowledgment

The author would like to express sincere gratitude to the medical staff and the medical records department of Chonburi Hospital for their invaluable support in collecting the data. Special thanks to the patients whose clinical data were included in this study, contributing to the advancement of lung cancer research in Thailand.

Author contributions

The author confirms sole responsible for the study's conceptualization, methodology, data curation, formal analysis, investigation, and writing the original draft, as well as reviewing and editing the final manuscript.

Data availability statement

The datasets analyzed during the current study are not publicly available due to hospital privacy policies and ethical restrictions regarding patient confidentiality but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study received approval from the Institutional Review Board of Chonburi Hospital, research code 2/67/S/h3, and exempted from obtaining informed consent due to the retrospective nature of the study design.

Clinical trial registration

Not applicable. This study was a retrospective chart review and was not registered as a clinical trial.

Use of artificial intelligence

During the preparation of this work, the author used generative AI (Gemini) to improve the grammatical accuracy and readability of the manuscript. The author has reviewed and edited the content and takes full responsibility for the integrity of the published article.

Funding disclosure

The present study received no specific grant from any funding agencies in the public, commercial, or not-for-profit sectors for the conduct of this study.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007;7:169-81.
2. Wu JY, Yu CJ, Chang YC, Yang CH, Shih JY, Yang PC. Effectiveness of tyrosine kinase inhibitors on "uncommon" epidermal growth factor receptor mutations of unknown clinical significance in non-small cell lung cancer. Clin Cancer Res 2011;17:3812-21.
3. Park S, Lee SY, Kim D, Sim YS, Ryu JS, Choi J, et al. Comparison of epidermal growth factor receptor tyrosine kinase inhibitors for patients with lung adenocarcinoma harboring different epidermal growth factor receptor mutation types. BMC Cancer 2021;21:52. doi: 10.1186/s12885-020-07765-6.
4. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2020;382:41-50.
5. Feinberg B, Halmos B, Gucalp R, Tang W, Moehring B, Hochmair MJ. Making the case for EGFR TKI sequencing in EGFR mutation-positive NSCLC: a GioTag study US patient analysis. Future Oncol 2020;16:1585-95.
6. Chang LC, Lim CK, Chang LY, Chen KY, Shih JY, Yu CJ. Non-small cell lung cancer harbouring non-resistant uncommon EGFR mutations: Mutation patterns, effectiveness of epidermal growth factor receptor-tyrosine kinase inhibitors and prognostic factors. Eur J Cancer 2019;119:77-86.
7. John T, Taylor A, Wang H, Eichinger C, Freeman C, Ahn MJ. Uncommon EGFR mutations in non-small-cell lung cancer: A systematic literature review of prevalence and clinical outcomes. Cancer Epidemiol 2022;76:102080. doi: 10.1016/j.canep.2021.102080.
8. Passaro A, Mok T, Peters S, Popat S, Ahn MJ, de Marinis F. Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations. J Thorac Oncol 2021;16:764-73.
9. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell

lung cancer. N Engl J Med 2018;378:113-25.
10. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol 2020;61:167-79.
11. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
12. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 2015;16:830-8.
13. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.
14. Wang C, Zhao K, Hu S, Dong W, Gong Y, Li M, et al. Clinical outcomes of gefitinib and erlotinib in patients with NSCLC harboring uncommon EGFR mutations: A pooled analysis of 438 patients. Lung Cancer 2022;172:86-93.
15. Tu HY, Ke EE, Yang JJ, Sun YL, Yan HH, Zheng MY, et al. A comprehensive review of uncommon EGFR mutations in patients with non-small cell lung cancer. Lung Cancer 2017;114:96-102.
16. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci 2016;107:1179-86.
17. Keam B, Kim DW, Park JH, Lee JO, Kim TM, Lee SH, et al. Rare and complex mutations of epidermal growth factor receptor, and efficacy of tyrosine kinase inhibitor in patients with non-small cell lung cancer. Int J Clin Oncol 2014;19:594-600.
18. De Pas T, Toffalorio F, Manzotti M, Fumagalli C, Spitaleri G, Catania C, et al. Activity of epidermal growth factor receptor-tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring rare epidermal growth factor receptor mutations. J Thorac Oncol 2011;6:1895-901.
19. Iyevleva AG, Mitiushkina NV, Karaseva NA, Orlov SV, Volodina LN, Kulikova YE, et al. Lung carcinomas with EGFR exon 19 insertions are sensitive to gefitinib treatment. J Thorac Oncol 2014;9:e31-3.
20. Klughammer B, Brugger W, Cappuzzo F, Ciuleanu T, Mok T, Reck M, et al. Examining treatment outcomes with erlotinib in patients with advanced non-small cell lung cancer whose tumors harbor uncommon EGFR mutations. J Thorac Oncol 2016;11:545-55.
21. Pilotto S, Rossi A, Vavalà T, Follador A, Tiseo M, Galetta D, et al. Outcomes of first-generation EGFR-TKIs against non-small-cell lung cancer harboring uncommon EGFR mutations: A post hoc analysis of the BE-POSITIVE study. Clin Lung Cancer 2018;19:93-104.
22. Cho JH, Lim SH, An HJ, Kim KH, Park KU, Kang EJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: A multicenter, open-label, phase II trial (KCSG-LU15-09). J Clin Oncol 2020;38:488-95.
23. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol 2018:Jco2018783118. doi: 10.1200/JCO.2018.78.3118.
24. Su PL, Wu YL, Chang WY, Ho CL, Tseng YL, Lai WW, et al. Preventing and treating brain metastases with three first-line EGFR-tyrosine kinase inhibitors in patients with EGFR mutation-positive advanced non-small cell lung cancer. Ther Adv Med Oncol 2018;10:1758835918797589. doi: 10.1177/1758835918797589.
25. Passaro A, Prelaj A, Bonanno L, Tiseo M, Tuzi A, Proto C, et al. Activity of EGFR TKIs in Caucasian patients with NSCLC harboring potentially sensitive uncommon EGFR mutations. Clin Lung Cancer 2019;20:e186-94.
26. Hata A, Yoshioka H, Fujita S, Kunimasa K, Kaji R, Imai Y, et al. Complex mutations in the epidermal growth factor receptor gene in non-small cell lung cancer. J Thorac Oncol 2010;5:1524-8.
27. Zhang B, Wang S, Qian J, Yang W, Qian F, Lu J, et al. Complex epidermal growth factor receptor mutations and their responses to tyrosine kinase inhibitors in previously untreated advanced lung adenocarcinomas. Cancer 2018;124:2399-406.
28. Lei L, Wang WX, Zhu YC, Li JL, Fang Y, Wang H, et al. Real-world efficacy and potential mechanism of resistance of icotinib in Asian advanced non-small cell lung cancer with EGFR uncommon mutations: A multi-center study. Cancer Med 2020;9:12-8.
29. Borgeaud M, Parikh K, Banna GL, Kim F, Olivier T, Le X, et al. Unveiling the landscape of uncommon EGFR mutations in NSCLC-A systematic review. J Thorac Oncol 2024;19:973-83.
30. Nogami N, Barlesi F, Socinski MA, Reck M, Thomas CA, Cappuzzo F, et al. IMpower150 final exploratory analyses for atezolizumab plus bevacizumab and chemotherapy in key NSCLC patient subgroups with EGFR mutations or metastases in the liver or brain. J Thorac Oncol 2022;17:309-23.
31. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.