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Original Article

# Epidermal Growth Factor Receptor Exon 19 Deletion Subtypes Do Not Influence Survival Outcomes Following First-line Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitors in Advanced Nonsmall Cell Lung Cancer Patients

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## Abstract

**Background:** Several deletion and insertion subtypes occur in exon 19 of the epidermal growth factor receptor (EGFR) gene, collectively called exon 19 deletions (del19), and are one of the common EGFR mutations in nonsmall cell lung cancer (NSCLC). Previous studies have shown that del19 subtypes might influence the response to tyrosine kinase inhibitors (TKIs), but their findings have been inconsistent. Therefore, this study aimed to evaluate the impact of del19 subtypes in an Asian population and provide additional evidence on this issue. **Materials and Methods:** NSCLC patients treated at Chang Gung Medical Hospitals between 2011 and 2018 were retrospectively reviewed. Their clinicopathological characteristics, clinical tumor response, progression-free survival (PFS), and overall survival (OS) were collected. PFS was evaluated among different del19 subtypes and EGFR-TKIs. **Results:** This study included 164 patients with NSCLC carrying an EGFR del19 mutation who had detailed information about their del19 subtype and were treated with frontline EGFR-TKIs (39 with afatinib and 125 with gefitinib/erlotinib). In this cohort, del19 subtypes did not influence PFS and OS based on different classifications, including start codon of deletion, the number of deleted nucleotides, or pure deletion versus mixed deletion/insertion/substitution. In addition, afatinib generally showed better PFS than gefitinib/erlotinib, particularly and significantly for patients with the p. E746_A750 mutation, a common 15 nucleotide deletion, or a pure deletion without insertion/substitution. **Conclusion:** In this study, del19 subtypes did not influence PFS and OS with EGFR-TKIs. Afatinib showed better activity than first-generation TKIs and should be preferred for patients with del19 mutations.

**Keywords:** Afatinib, epidermal growth factor receptor, erlotinib, exon 19 deletion, gefitinib, nonsmall cell lung cancer, tyrosine kinase inhibitor

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## Introduction

Lung cancer is the leading cause of global cancer mortality.[1] Mutations in the epidermal growth factor receptor (EGFR) gene are the most common oncogenic divers in nonsmall cell lung cancer (NSCLC), and their frequency is ethnicity-dependent: 20%–76% in Asians, 3%–42% in white Americans, and 6%–41% in Europeans.[2,3] In-frame deletions (dels) in exon 19 (del19) and the L858R mutation in exon 21 account for most EGFR mutations and are collectively called common EGFR mutations,[4,5] with other mutations called uncommon mutations.[6,7] Del19 encompasses many genetic variants reflecting in-frame dels starting at different codons, with or without substitutions (subs) or insertions (ins), that may influence the efficacy of tyrosine kinase inhibitors (TKIs).

The E746_A750 del starting at E746 and ending at A750 belongs to the E746 del subtype (del from E746) and is the most common del19 mutation,[8] accounting for >60% of del19 mutations. After E746_A750, another common del is L747_T751, belonging to the L747 del subtype. Both E746_A750 and L747_T751 are common dels of 15 nucleotides (common 15n-del), and the other subtypes include uncommon 15n-del and 18n-del mutations. In addition, some variants have additional ins or subs. These EGFR del19 subtypes differ in molecular structure and possibly in response to EGFR-TKIs. One study found that patients with dels starting at E746 had significantly longer overall survival (OS) and relatively but not significantly longer progression-free survival (PFS) than those with dels starting at L747.[8] However, other studies have not shown the same results,[9-11] indicating some inconsistency in the results of previous studies.

Therefore, further exploration of del19 subtypes and their associated clinical outcomes is warranted. In this study, we comprehensively evaluated the impact of different del19 subtypes on first-line EGFR-TKI treatment in patients with NSCLC based on commonly used grouping approaches: common (E746_A750 and L747_T751) versus uncommon dels, initial del codon (E746 vs. L747), the number of deleted nucleotides (15n-del vs. 18n-del), and the presence of dels/ins/subs. In addition, we evaluated the activity of different EGFR-TKIs with different del19 variants.

## Materials and Methods

### Patients and data collection

All patients' data were obtained from the cancer registry system using the Chang Gung Research Database.[4,12,13] Patients with a lung cancer diagnosis and a documented EGFR mutation treated with first-line EGFR-TKI monotherapy between January 2011 and January 2018 were retrospectively reviewed.[14] During the study period, EGFR status was measured using Sanger sequencing or polymerase chain reaction (PCR)-based methods. PCR-based methods cannot determine del19 subtypes. Only patients with detailed Sanger sequencing reports for del19 subtypes were included in the analysis; patients with active cancer were excluded. Since this study aimed to examine patients given EGFR-TKI monotherapy as their first-line systemic treatment, those patients treated with concurrent chemotherapy, concurrent anti-angiogenesis, and later-line systemic treatment were excluded.

The clinical characteristics of patients given EGFR-TKIs as first-line treatments were retrospectively reviewed. The clinicopathological features reviewed included age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status score, stage, TKI use, tumor morphology, tumor involvement, del19 subtype, and tumor response. The last follow-up time point in this study was May 2021.

### Treatment and response evaluation

Patients were treated with first-line EGFR-TKI until disease progression, intolerable toxicity, or death from all causes. The EGFR-TKI dose and treatment schedule were adjusted by physicians based on the patient's clinical condition and adverse events.

The tumor response was evaluated by chest X radiography and computed tomography and determined according to the response evaluation criteria in solid tumors 1.1. The best clinical tumor response was recorded as complete response, partial response, stable disease, or progressive disease. Any tumor response not assessed (NA) before death or discontinuation was recorded as "NA."

PFS was defined as the duration from the 1st day of EGFR-TKI treatment until the first radiological evidence of disease progression, the last dose of EGFR-TKI, death, or the last follow-up time point. Patients who experienced radiological progression or death within 1 month of EGFR-TKI discontinuation and received no sequential treatment were

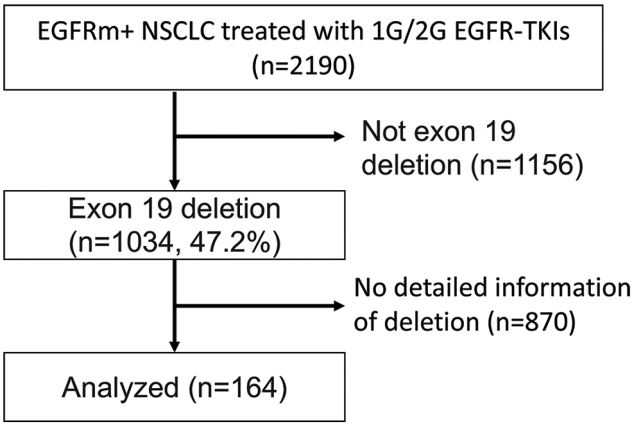


**Figure 1:** Overview of study search and selection. A total of 2190 epidermal growth factor receptor (EGFR) mutated nonsmall cell lung cancer (NSCLC) patients treated with 1G/2G EGFR-tyrosine kinase inhibitors as first-line treatment were reviewed in this study, and 1034 patients with NSCLC harboring EGFR del19 were treated with frontline EGFR-TKIs were included. Only 164 patients (39 treated with afatinib, 125 treated with gefitinib/erlotinib) had detailed information of del19 which can be analyzed. NSCLC: Non-small cell lung cancer, EGFR-TKI: Epidermal growth factor receptor tyrosine kinase inhibitor, Del19: Deletion 19

considered an event. OS was defined as the duration from the 1st day of first-line EGFR-TKI treatment until death or the last follow-up time point. The data of living patients were masked during the survival analysis.

## Statistical analysis

Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test based on expected values. Survival was assessed using Kaplan–Meier curves, and the log-rank test was used to compare survival between subgroups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression analysis. All statistical analyses were performed with IBM SPSS statistics for windows (version 23.0, Armonk, NY, USA). Statistical significance was set at $P < 0.05$. Survival curves were plotted using R software (R version 4.0.5, R Core Team, 2021, R Foundation for Statistical Computing, Vienna, Austria). Forest plots were created with Graph Pad Prism 5.0 (Graph Pad Software Inc., La Jolla, CA, USA).

## Ethical issue

This study was approved by the Institutional Review Board of CGMH (201901395B0C501). Since this was a retrospective study, patient informed consent was not required.

# Results

## Patients' characteristics

This study reviewed 2190 patients with EGFR-mutated NSCLC given first (1G) or second (2G) generation EGFR-TKIs as first-line treatment, including 1034 patients with NSCLC and EGFR del19 mutations treated with frontline EGFR-TKIs. Only 164 patients (39 treated with afatinib and 125 treated with gefitinib/erlotinib) had detailed information about their del19 mutation [Figure 1]. Patients treated with afatinib had a younger median age than those treated with gefitinib/erlotinib (58 vs. 67 years; $P < 0.001$). The afatinib and gefitinib/erlotinib groups did not differ significantly except for the mutation start codon (p. E746, p. L747, and other: 69.2%, 23.1%, and 7.7%

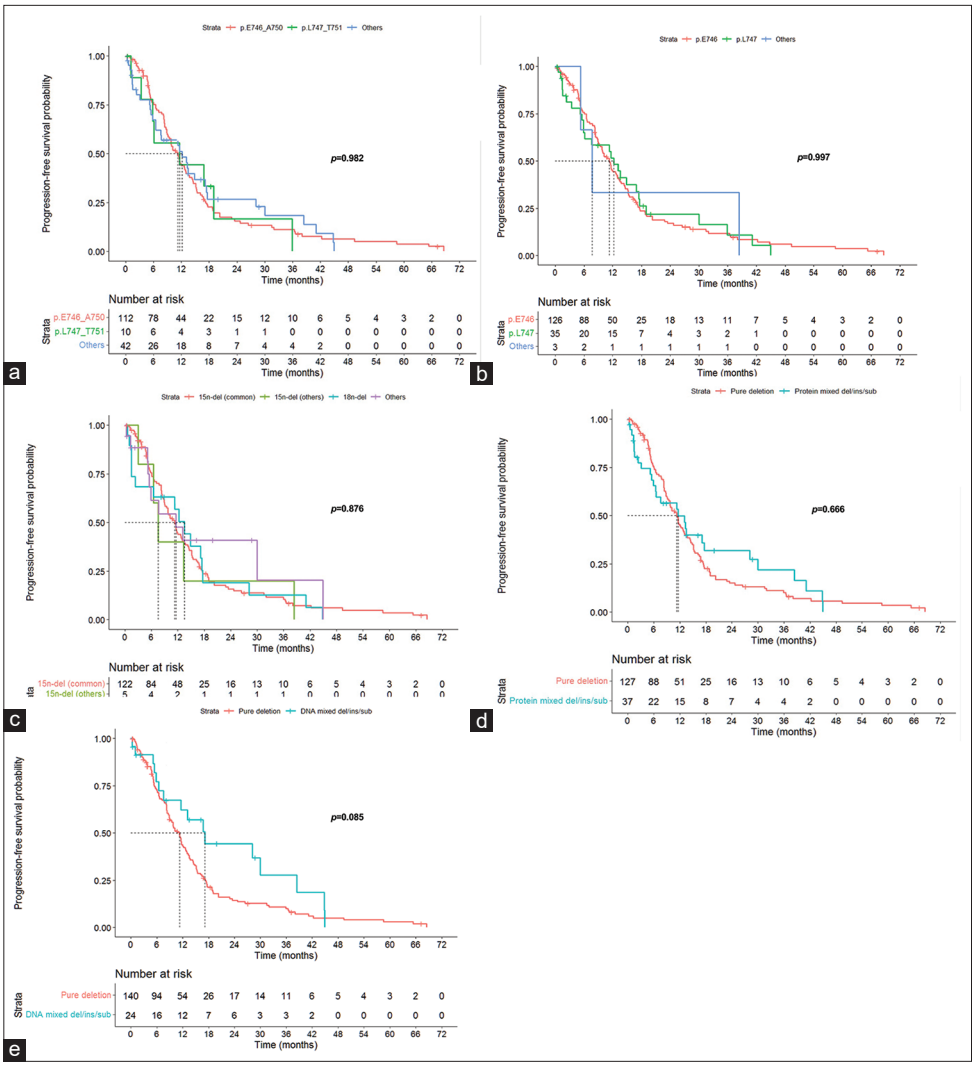


**Figure 2:** Del19 subtypes did not influence PFS based on different classification. (a) Common deletion of 15 nucleotides, (b) the start codon of deletion (c) the number of deleted nucleotides, (d and e) pure deletion versus mixed protein or DNA deletion/insertion/substitution. Del19: Deletion 19, PFS: Progression free survival

vs. 79.2%, 20.8%, and 0%, respectively; $P = 0.006$) and dose reduction [35.9% vs. 5.6%; $P < 0.0001$; Table 1].

## The influence of 19 deletion subtypes on epidermal growth factor receptor -tyrosine kinase inhibitors

In this cohort, del19 subtypes did not influence PFS and OS based on different classifications, including common 15n-del, the del's start codon, the number of deleted nucleotides, or pure del versus mixed protein/DNA del/ins/sub [Figures 2 and 3]. Forest plot of hazard ratio for progression-free and survival overall survival showed preferring afatinib group which is summarized in [Figure 4].

## The influence of epidermal growth factor receptor-tyrosine kinase inhibitors on exon 19 deletion subtypes

Overall, afatinib conferred significantly longer PFS than gefitinib/erlotinib in all patients (median = 15.1 vs. 9.8 months, log-rank $P = 0.039$; HR = 0.67, 95% CI = 0.46–0.98, $P = 0.04$) and in those with p. E746_A750 (median = 15.1 vs. 9.1 months, log-rank $P = 0.047$; HR = 0.63, 95% CI = 0.40-0.99, $P = 0.049$), common 15n-del (median = 15.4 vs. 9.0 months, log-rank $P = 0.029$; HR = 0.62, 95% CI = 0.40–0.95, $P = 0.030$), and pure del without DNA/protein ins/sub (HR = 0.65, 95% CI = 0.43–0.97, $P = 0.035$) mutations. The influence of EGFR-TKIs on PFS based on del19 subtypes is summarized in Table 2 and Figure 5.

In addition, afatinib conferred longer OS than gefitinib/erlotinib in all patients (median = 32.3 vs. 15.3 months, log-rank $P < 0.001$; HR = 0.49, 95% CI = 0.33–0.73, $P < 0.001$) and those with p. E746_A750 (median = 32.3 vs. 16.4 months, log-rank $P = 0.05$; HR = 0.50, 95% CI = 0.30–0.82, $P = 0.006$), p. L747_T751 (median = 48.4 vs. 7.7 months, log-rank $P = 0.009$; HR = 0.06, 95% CI = 0.01–0.53, $P = 0.007$), p. E746 start codon (median = 32.3 vs. 16.4 months, log-rank $P = 0.005$; HR = 0.51, 95% CI = 0.32–0.83, $P = 0.006$),

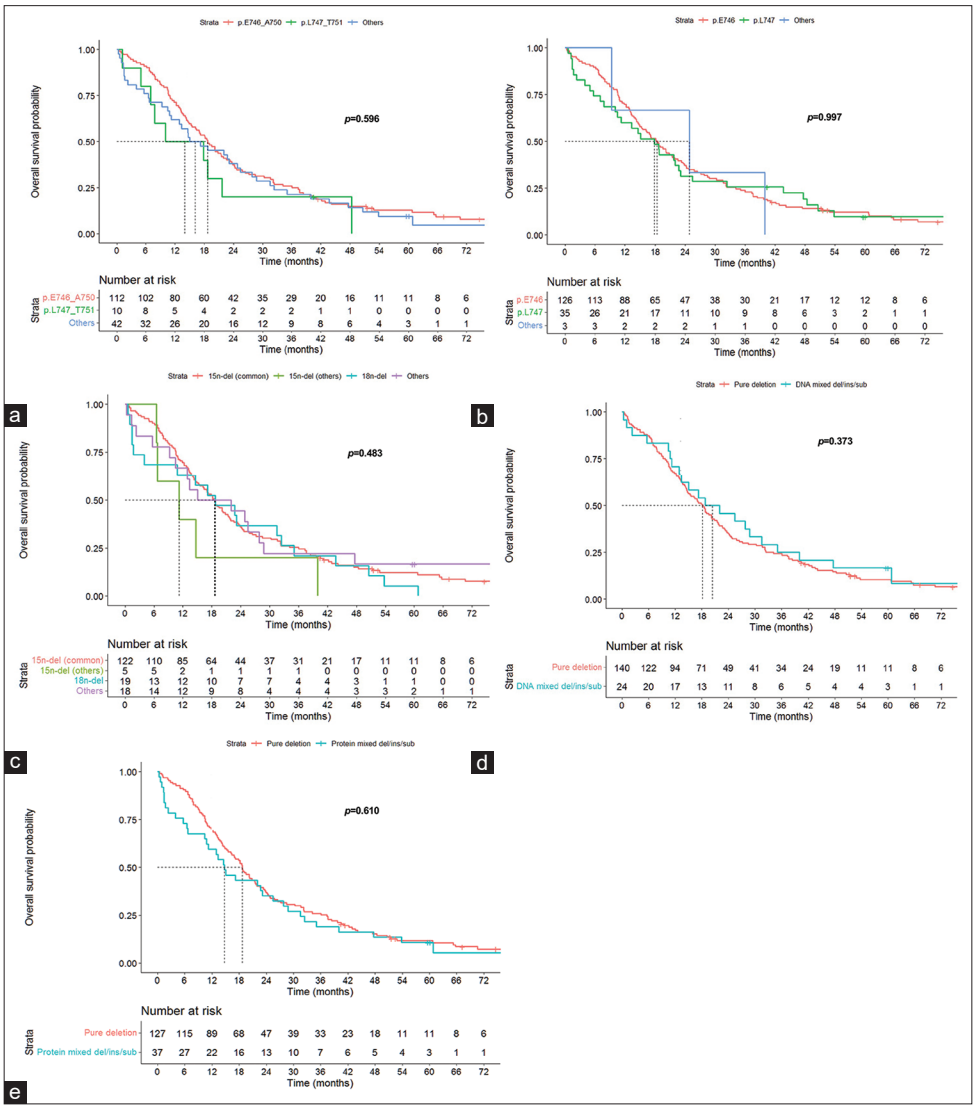


**Figure 3:** Del19 subtypes did not influence overall survival based on different classification (a) 15n-del, (b) the start codon of deletion, (c) the number of deleted nucleotides, (d and e) pure deletion versus mixed protein or DNA deletion/insertion/substitution. Del19: Deletion 19, 15n-del: Common deletion of 15 nucleotides, OS: Overall survival

**Table 1: Characteristics of patients with nonsmall cell lung cancer carrying an epidermal growth factor receptor exon 19 deletions mutation (*n*=164) treated with afatinib or gefitinib/erlotinib**

| Characteristics | *n* (%) | Afatinib (*n*=39) | Gefitinib/erlotinib (*n*=125) | *P* |
|---|---|---|---|---|
| Age (years) | | | | <0.001 |
| Median (range) | 164 (34–95) | 58 (38–87) | 67 (34–95) | |
| Gender | | | | 0.054 |
| Male | 68 (41.5) | 11 (28.2) | 57 (45.6) | |
| Female | 96 (58.5) | 28 (71.8) | 68 (54.4) | |
| ECOG performance | | | | 0.054 |
| 0–1 | 124 (75.6) | 34 (87.2) | 90 (72.0) | |
| 2–4 | 40 (24.4) | 5 (12.8) | 35 (28.0) | |
| Smoking | | | | 0.213 |
| No | 112 (68.3) | 31 (79.5) | 81 (64.8) | |
| Yes | 51 (31.1) | 8 (19.4) | 43 (34.4) | |
| Unknown | 1 (0.6) | 0 | 1 (0.8) | |
| Histology | | | | 0.573 |
| Adenocarcinoma | 160 (97.6) | 39 (100.0) | 121 (96.8) | |
| Adenosquamous | 4 (2.4) | 0 | 4 (2.4) | |
| Stage | | | | 0.199 |
| IIIB | 7 (4.3) | 0 | 7 (5.6) | |
| IV | 157 (95.7) | 39 (100.0) | 118 (94.4) | |
| Types of mutation | | | | 0.890 |
| p.E746_A750 | 112 (68.3) | 26 (66.7) | 86 (68.8) | |
| p.L747_T751 | 10 (6.1) | 3 (7.7) | 7 (5.6) | |
| Others | 42 (25.6) | 10 (25.6) | 32 (25.6) | |
| Types of mutation | | | | 0.006 |
| p.E746 | 126 (76.8) | 27 (69.2) | 99 (79.2) | |
| p.L747 | 35 (21.3) | 9 (23.1) | 26 (20.8) | |
| Others | 3 (1.8) | 3 (7.7) | 0 | |
| Types of mutation | | | | 0.670 |
| 15n-del (common) | 122 (74.4) | 29 (74.4) | 93 (74.4) | |
| 15n-del (others) | 5 (3.0) | 2 (5.1) | 3 (2.4) | |
| 18n-del | 19 (11.6) | 3 (7.7) | 16 (12.8) | |
| Others | 18 (11.0) | 5 (12.8) | 13 (10.4) | |
| Types of mutation | | | | 0.430 |
| Protein mixed del/ins/sub | 37 (22.6) | 7 (17.9) | 30 (24.0) | |
| Pure deletion | 127 (77.4) | 32 (82.1) | 95 (76.0) | |
| Types of mutation | | | | 0.376 |
| DNA mixed del/ins/sub | 24 (14.6) | 4 (10.3) | 20 (16.0) | |
| Pure deletion | 140 (85.4) | 35 (89.7) | 105 (84.0) | |
| Dose reduction | | | | <0.0001 |
| Yes | 21 (12.8) | 14 (35.9) | 7 (5.6) | |
| No | 143 (87.2) | 25 (64.1) | 118 (94.4) | |
| Discontinuation | | | | >0.999 |
| Yes | 9 (5.5) | 2 (5.1) | 7 (5.6) | |
| No | 155 (94.5) | 37 (94.9) | 118 (94.4) | |
| Lung metastasis | | | | 0.071 |
| Yes | 53 (32.3) | 8 (20.5) | 45 (36.0) | |
| No | 111 (67.7) | 31 (79.5) | 80 (64.0) | |
| Liver metastasis | | | | 0.748 |
| Yes | 28 (17.1) | 6 (15.4) | 22 (17.6) | |
| No | 136 (82.9) | 33 (84.6) | 103 (82.4) | |
| Brain metastasis | | | | 0.397 |
| Yes | 58 (35.4) | 16 (41.0) | 42 (33.6) | |
| No | 106 (64.6) | 23 (59.0) | 83 (66.4) | |

*Contd...*

**Table 1: Contd...**

| Characteristics | *n* (%) | Afatinib (*n*=39) | Gefitinib/erlotinib (*n*=125) | *P* |
|---|---|---|---|---|
| Bone metastasis | | | | 0.787 |
| Yes | 81 (49.4) | 20 (51.3) | 61 (48.8) | |
| No | 83 (50.6) | 19 (48.7) | 64 (51.2) | |
| Pleural metastasis | | | | 0.923 |
| Yes | 81 (49.4) | 19 (48.7) | 62 (49.6) | |
| No | 83 (50.6) | 20 (51.3) | 63 (50.4) | |
| Adrenal metastasis | | | | 0.581 |
| Yes | 21 (12.8) | 6 (15.4) | 15 (12.0) | |
| No | 143 (87.2) | 33 (84.6) | 110 (88.0) | |
| Distant lymph node metastasis | | | | 0.378 |
| Yes | 18 (11.0) | 6 (15.4) | 12 (9.6) | |
| No | 146 (89.0) | 33 (84.6) | 113 (90.4) | |
| Response | | | | 0.535 |
| PR | 111 (67.7) | 28 (71.8) | 83 (66.4) | |
| SD | 26 (15.9) | 6 (15.4) | 20 (16.0) | |
| PD | 9 (5.5) | 3 (7.7) | 6 (4.8) | |
| N/A | 18 (11.0) | 2 (5.1) | 16 (12.8) | |

Values in parentheses are percentages. ECOG: Eastern Cooperative Oncology Group, PR: Partial response, SD: Stable disease, PD: Progressive disease, NA: Not available

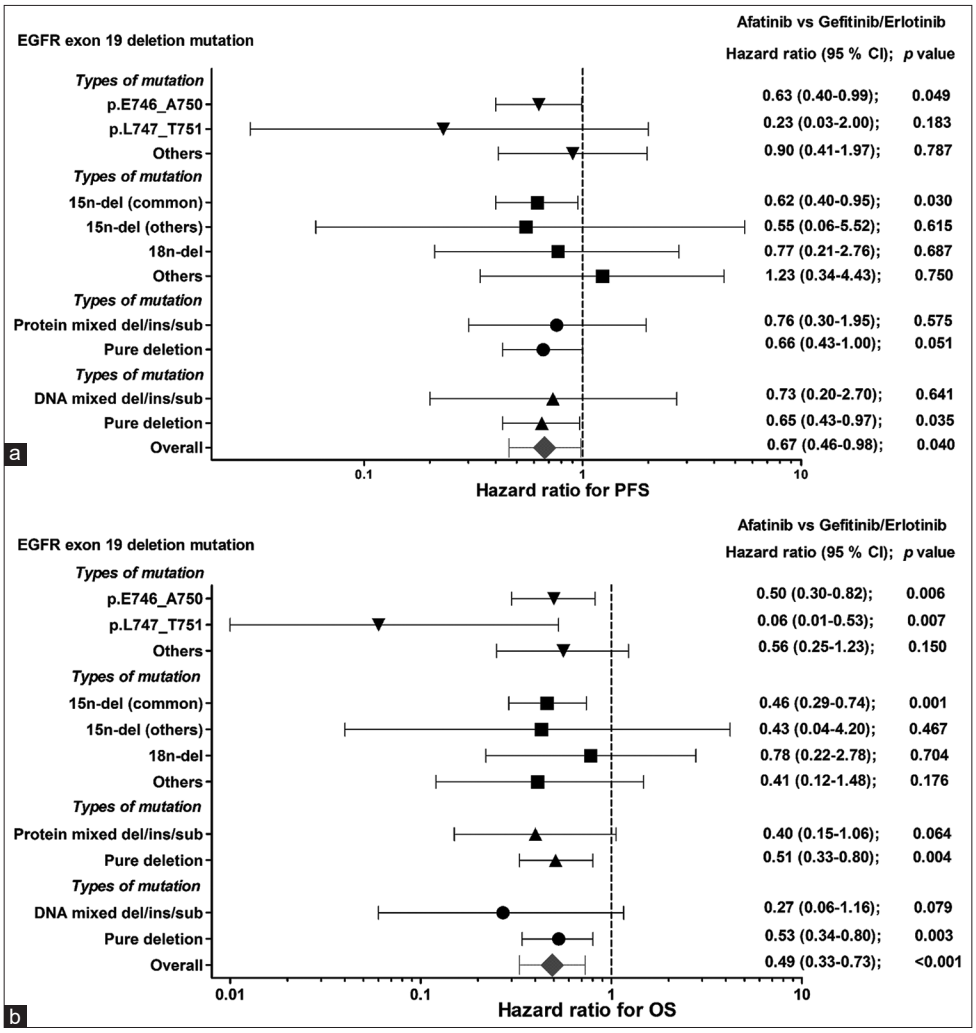


**Figure 4:** Forest plot of hazard ratio for (a) progression-free survival (b) overall survival

p. L747 start codon (median = 48.4 vs. 11.2 months, log-rank $P = 0.010$; HR = 0.32, 95% CI = 0.13–0.79, $P = 0.014$), common 15n-del (median = 34.2 vs. 16.2 months, log-rank $P = 0.001$; HR = 0.46, 95% CI = 0.29–0.74, $P = 0.001$), and pure del without ins/sub (HR = 0.53, 95% CI = 0.34–0.80, $P = 0.003$) mutations. The influence of EGFR-TKIs on OS based on del19 subtypes is summarized in Table 3 and Figure 6.

Patients treated with afatinib were significantly younger and had good ECOG performance status, although not significant, and a higher proportion of them were female than those treated with gefitinib/erlotinib. These characteristics may influence the efficacy of afatinib. Therefore, univariate and multivariant analyses were performed. Age (continuous/categorical variables), ECOG performance status, and female sex were not significant prognostic factors of PFS; therefore, multivariate analysis was not performed [Table 4]. The OS of the afatinib group was better than that of the gefitinib/erlotinib group after being adjusted for age, ECOG performance status, and gender [Table 5].

## Discussion

This study examined 164 patients with NSCLC carrying a del19 mutation treated with afatinib or gefitinib/erlotinib. Their PFS and OS did not differ significantly by del19 subtype (common 15n-del, 18–nucleotide del, pure del, protein mixed del/ins/sub, and DNA mixed del/ins/sub) or del19 start codon (E746 vs. L747). Moreover, afatinib conferred better PFS and OS for patients with NSCLC carrying almost all del19 mutation variants.

While a few studies have reported differences in sensitivity to EGFR-TKIs among patients with different del19 subtypes, their findings were inconclusive. According to the database of somatic mutations in EGFR and previous studies, the most frequent del19 mutations are p. E746_A750 (74%) and p. L747_P751 (7.3%).[15,16] Moreover, two studies have shown that p. E746_A750 is the predominant del19 subtype with a higher T790M mutation rate and better PFS and OS.[8,17] However, other studies have shown no significant difference in PFS and OS.[18,19] In our study, p. E746_A750 was the predominant subtype, the same as in the above database. However, our study supported no significant difference between del19 subtypes with a larger case number than the previous study.

In Taiwan, 1G/2G EGFR-TKIs gefitinib, erlotinib, and afatinib are commonly prescribed as frontline therapy for patients with EGFR-mutated NSCLC.[20,21] The 1G TKIs gefitinib and erlotinib are reversible inhibitors of both wild type EGFR and EGFR with common mutations.[22-24] Two head-to-head trials (CTONG0901 and WJOG5108 L) found no significant differences in PFS, OS, and overall response rate between them.[25,26] The 2G EGFR-TKI afatinib is an irreversible EGFR-TKI for wildtype and mutant EGFR.[22] The LUX-lung 7 phase IIb trial found that afatinib conferred significantly better PFS and tended to confer better OS than gefitinib.[27]

**Table 2: The progression-free survival of patients treated with afatinib versus gefitinib/erlotinib based on their exon 19 deletions subtype**

| EGFR exon del19 mutation | *n* | HR* (95% CI) | *P* |
|---|---|---|---|
| Types of mutation | | | |
| p.E746_A750 | 112 | 0.63 (0.40–0.99) | 0.049 |
| p.L747_T751 | 10 | 0.23 (0.03–2.00) | 0.183 |
| Others | 42 | 0.90 (0.41–1.97) | 0.787 |
| Types of mutation | | | |
| p.E746 | 126 | 0.69 (0.44–1.08) | 0.107 |
| p.L747 | 35 | 0.54 (0.22–1.29) | 0.164 |
| Others | 3 | NA (all afatinib) | - |
| Types of mutation | | | |
| 15n-del (common) | 122 | 0.62 (0.40–0.95) | 0.030 |
| 15n-del (others) | 5 | 0.55 (0.06–5.52) | 0.615 |
| 18n-del | 19 | 0.77 (0.21–2.76) | 0.687 |
| Others | 18 | 1.23 (0.34–4.43) | 0.750 |
| Types of mutation | | | |
| Protein mixed del/ins/sub | 37 | 0.76 (0.30–1.95) | 0.575 |
| Pure deletion | 127 | 0.66 (0.43–1.00) | 0.051 |
| Types of mutation | | | |
| DNA mixed del/ins/sub | 24 | 0.73 (0.20–2.70) | 0.641 |
| Pure deletion | 140 | 0.65 (0.43–0.97) | 0.035 |
| Overall | 164 | 0.67 (0.46–0.98) | 0.040 |

*Gefitinib/erlotinib as reference. EGFR: Epidermal growth factor receptor, CI: Confidence interval, NA: Not available, HR: Hazard ratio, del19: 19 deletions

**Table 3: The overall survival of patients treated with afatinib versus gefitinib/erlotinib based on their exon 19 deletions subtype**

| EGFR exon del19 mutation | *n* | HR* (95% CI) | *P* |
|---|---|---|---|
| Types of mutation | | | |
| p.E746_A750 | 112 | 0.50 (0.30–0.82) | 0.006 |
| p.L747_T751 | 10 | 0.06 (0.01–0.53) | 0.007 |
| Others | 42 | 0.56 (0.25–1.23) | 0.150 |
| Types of mutation | | | |
| p.E746 | 126 | 0.51 (0.32–0.83) | 0.006 |
| p.L747 | 35 | 0.32 (0.13–0.79) | 0.014 |
| Others | 3 | NA (all afatinib) | - |
| Types of mutation | | | |
| 15n-del (common) | 122 | 0.46 (0.29–0.74) | 0.001 |
| 15n-del (others) | 5 | 0.43 (0.04–4.20) | 0.467 |
| 18n-del | 19 | 0.78 (0.22–2.78) | 0.704 |
| Others | 18 | 0.41 (0.12–1.48) | 0.176 |
| Types of mutation | | | |
| Protein mix/del/ins/sub | 37 | 0.40 (0.15–1.06) | 0.064 |
| Pure deletion | 127 | 0.51 (0.33–0.80) | 0.004 |
| Types of mutation | | | |
| DNA mix/del/ins/sub | 24 | 0.27 (0.06–1.16) | 0.079 |
| Pure deletion | 140 | 0.53 (0.34–0.80) | 0.003 |
| Overall | 164 | 0.49 (0.33–0.73) | <0.001 |

*Gefitinib/erlotinib as reference. EGFR: Epidermal growth factor receptor, CI: Confidence interval, NA: Not available, HR: Hazard ratio, del19: 19 deletions

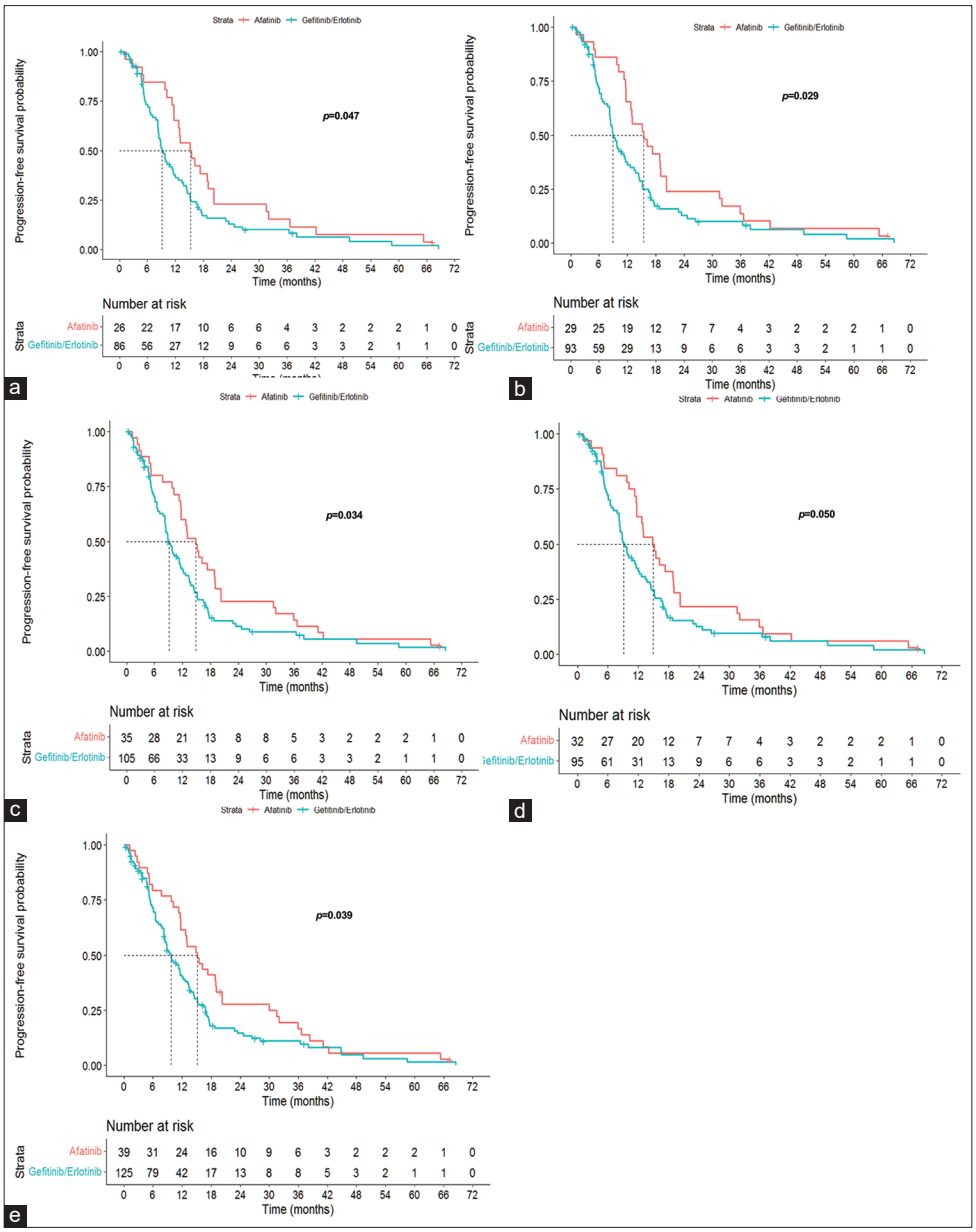


**Figure 5:** Afatinib significantly exhibited longer PFS than gefitinib/erlotinib for (a) start codon p. E746_A750, (b) 15n-del (common), (c) pure deletion DNA, (d) pure deletion protein, (e) overall patients. PFS: Progression free survival, 15n-del19 (common): Common deletion of 15 nucleotides

In our study, afatinib conferred better PFS and OS than 1G EGFR-TKIs regardless of the del19 subtype. Therefore, afatinib should be preferred for patients with NSCLC carrying a del19 mutation.

This retrospective study had some limitations. First, it only included a small number of patients since only a few tumors had detailed information on their del19 mutation. However, this study included more cases than previous studies, which can provide more convincing evidence. Second, as afatinib was more efficacious than gefitinib/erlotinib, the impact of the del19 subtypes should be analyzed under the same EGFR-TKI. However, due to the limited number of cases in this study, comparison of del19 subtypes under the same TKI treatment would not yield a convincing result. Third, this study did not analyze acquired T790M mutations, an important resistance mutation for del19 mutations. This omission was primarily due to recent del19 mutations being detected using PCR-based methods that do not provide detailed information. Most of our enrolled cases whose EGFR status was detected by Sanger sequencing were treated before the osimertinib era. Therefore, T790M testing was not a standard of care after tumor progression.

## Conclusion

In this study, del19 subtypes did not influence PFS or OS with EGFR-TKIs. Afatinib showed better activity than 1G TKIs and should be preferred for patients with del19 mutations regardless of their exact variant.

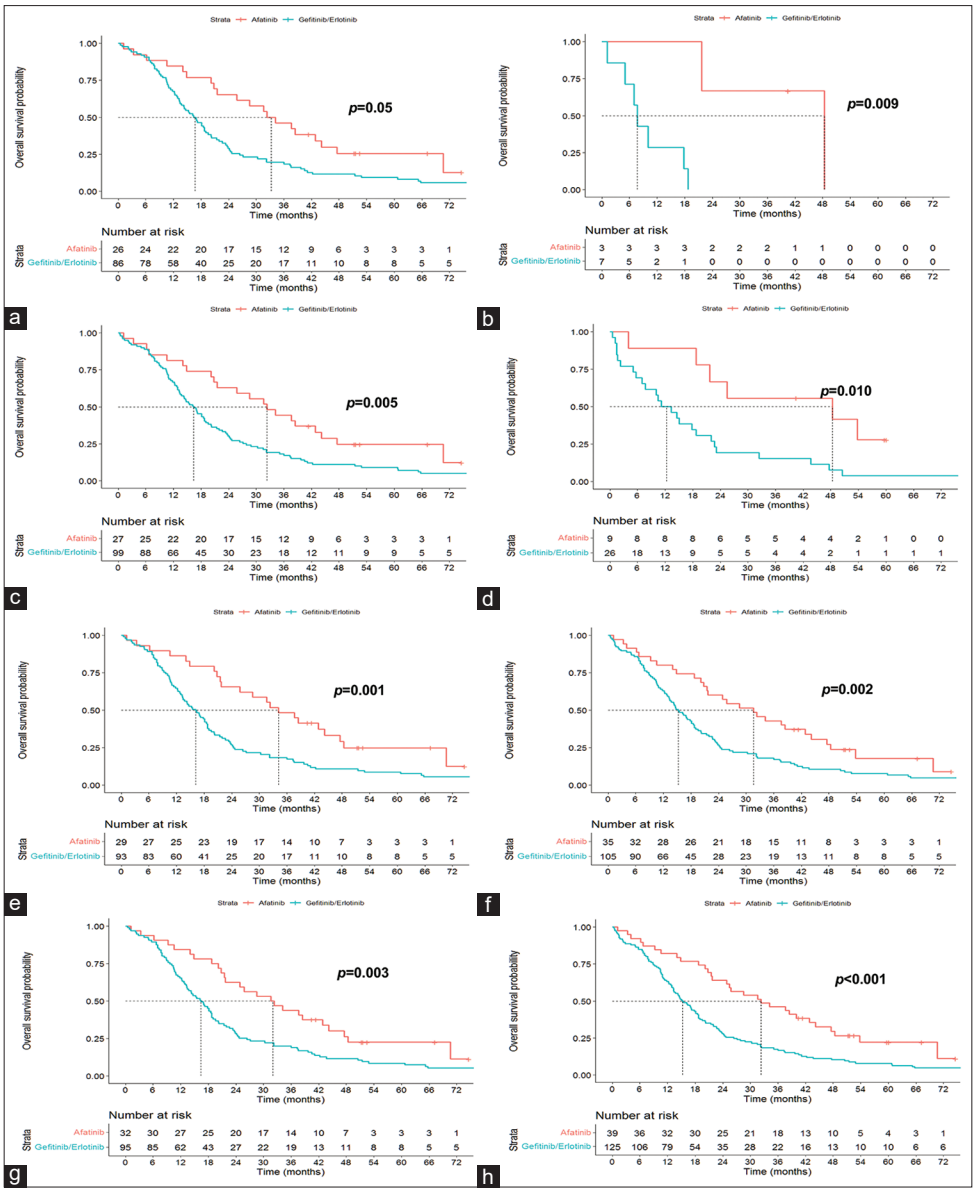


**Figure 6:** Afatinib significantly exhibited longer overall survival than gefitinib/erlotinib for (a) start codon p. E746_A750, (b) start codon p. E747_A751, (c) start codon p. E746, (d) start codon p. E747, (e) 15n-del (common), (f) pure deletion DNA, (g) pure deletion protein, (h) overall patients. OS: Overall survival, 15n-del19 (common): Common deletion of 15 nucleotides

**Table 4: Univariate analysis of progression-free survival**

| Characteristic | HR | 95% CI of HR | *P* |
|---|---|---|---|
| Age (years) | 1.002* | 0.984–1.012 | 0.743 |
| <65 | Reference | | |
| ≥65 | 1.008 | 0.719–1.413 | 0.965 |
| Gender | | | |
| Male | 1.283 | 0.912–1.805 | 0.152 |
| Female | Reference | | |
| ECOG performance | | | |
| 0–1 | Reference | | |
| 2–4 | 1.263 | 0.851–1.874 | 0.247 |
| TKI | | | |
| Afatinib | Reference | | |
| Gefitinib/erlotinib | 1.491 | 1.018–2.184 | 0.040 |

*0.2% increase in the progression rate for every 1-year increase in age. ECOG: Eastern Cooperative Oncology Group, TKI: Tyrosine kinase inhibitor, HR: Hazard ratio, CI: Confidence interval

**Table 5: Univariate and multivariate analyses of overall survival**

| Characteristic | HR | *P* | Adjusted HR# | *P* | Adjusted HR$ | *P* |
|---|---|---|---|---|---|---|
| Age (years) | 1.016* | 0.021 | | | 1.002 | 0.774 |
| <65 | Reference | | Reference | | | |
| ≥65 | 1.458 | 0.020 | 1.142 | 0.452 | | |
| Gender | | | | | | |
| Male | 1.572 | 0.006 | 1.560 | 0.010 | 1.545 | 0.012 |
| Female | Reference | | Reference | | Reference | |
| ECOG performance | | | | | | |
| 0–1 | Reference | | Reference | | Reference | |
| 2–4 | 1.894 | <0.001 | 1.910 | 0.001 | 1.949 | 0.001 |
| TKI | | | | | | |
| Afatinib | Reference | | Reference | | Reference | |
| Gefitinib/erlotinib | 2.043 | <0.001 | 1.663 | 0.021 | 1.705 | 0.016 |

*1.6% increase in the mortality rate for every 1-year increase in age, #Adjusted by age (categorical variable), $Adjusted by age (continuous variable).
ECOG: Eastern Cooperative Oncology Group, TKI: Tyrosine kinase inhibitor, HR: Hazard ratio

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## Conflicts of interest

Dr. Chiao-En Wu , an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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