Original Article

Real-world first-line afatinib for advanced *EGFR* mutation-positive non-small cell lung cancer in Korea: updated survival data

Juwhan Choi[1], Chang Min Choi[2], Yoon Soo Chang[3], Kye Young Lee[4], Seung Joon Kim[5], Sei Hoon Yang[6], Jeong Seon Ryu[7], Jeong Eun Lee[8], Shin Yup Lee[9], Ji Young Park[10], Young-Chul Kim[11], In-Jae Oh[11], Chi Young Jung[12], Sang Hoon Lee[13], Seong Hoon Yoon[14], Sung Yong Lee[1], Tae Won Jang[15]

[1]Division of Pulmonary, Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea; [2]Department of Pulmonary and Critical Care Medicine, Ulsan University Asan Medical Center, Seoul, South Korea; [3]Division of Pulmonary, Department of Internal Medicine, Yonsei University Gangnam Severance Hospital, Seoul, South Korea; [4]Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, South Korea; [5]Division of Pulmonary, Department of Internal Medicine, Catholic University Seoul St. Mary's Hospital, Seoul, South Korea; [6]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Wonkwang University Hospital, Iksan, South Korea; [7]Division of Pulmonary, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea; [8]Division of Pulmonary, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea; [9]Division of Pulmonary, Department of Internal Medicine, Kyungpook National University, Daegu, South Korea; [10]Division of Pulmonary, Allergy and Critical Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, South Korea; [11]Department of Internal Medicine, Chonnam National University Medical School and Hwasun Hospital, Hwasun, South Korea; [12]Division of Pulmonary, Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu, South Korea; [13]Division of Pulmonary, Department of Internal Medicine, Yonsei University Severance Hospital, Seoul, South Korea; [14]Division of Pulmonary, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea; [15]Division of Pulmonary, Department of Internal Medicine, Kosin University Gospel Hospital, Busan, South Korea

Contributions: (I) Conception and design: YS Chang, JS Ryu, Shin Yup Lee, Sung Yong Lee, JY Park, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (II) Administrative support: CM Choi, KY Lee, J Choi, TW Jang; (III) Provision of study materials or patients: CM Choi, YS Chang, KY Lee, YC Kim, CY Jung, SH Yoon, TW Jang; (IV) Collection and assembly of data: CM Choi, KY Lee, JS Ryu, JY Park, J Choi, TW Jang; (V) Data analysis and interpretation: Shin Yup Lee, CM Choi, KY Lee, SJ Kim, SH Yang, JS Ryu, JE Lee, Sung Yong Lee, JY Park, IJ Oh, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tae Won Jang, MD. Division of Pulmonary, Department of Internal Medicine, Kosin University Gospel Hospital, 262 Gamchenro, Suh Gu, Busan 49267, South Korea. Email: jangtw22@hanmail.net.

Background: Data from clinical trials and real-world studies show that afatinib is effective in treating non-small cell lung cancer (NSCLC) harboring activating mutations in the epidermal growth factor receptor (*EGFR*) gene. A previous analysis of patients enrolled in the Korean Academy of Tuberculosis and Respiratory Disease (KATRD) *EGFR* cohort showed that first-line afatinib was well tolerated and effectiveness results were encouraging. At the time of the previous analysis, survival data were not mature. Here we briefly present updated survival data from the cohort.

Methods: The study was a retrospective, multicenter (15 sites) review of electronic records of Korean adult patients (aged >20 years) with advanced *EGFR* mutation-positive NSCLC who initiated first-line afatinib (N=421). Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan-Meier survival curves.

Results: Overall, median PFS was 20.2 months and median OS was 48.6 months. OS rates at 36 and 60 months were 60.1% and 42.3%, respectively. Presence *vs.* absence of baseline brain metastases was associated with significantly reduced median PFS (14.9 *vs.* 28.0 months; P<0.001) and median OS (32.2 *vs.* 65.6 months; P<0.001). The presence of common baseline *EGFR* mutations (Del19, L858R) was associated with significantly prolonged median OS (49.6 *vs.* 30.1 months; P=0.017). In patients stratified by the presence/absence of T790M *EGFR* mutation, the T790M mutation was associated with significantly reduced median PFS (P=0.0005) but there was no significant difference between groups in survival (P=0.263). There were no significant differences in PFS or OS for patients stratified by afatinib dose reduction or by age group (<70 *vs.* ≥70 years).

Conclusions: Afatinib was effective in Korean patients with *EGFR* mutation-positive NSCLC with median OS over 4 years. The presence of baseline brain metastases and/or uncommon *EGFR* mutations were associated with reduced survival. In the absence of baseline brain metastases, median OS was more than 5 years.

Keywords: Afatinib; epidermal growth factor receptor (EGFR); first-line; non-small cell lung cancer (NSCLC); real-world

Submitted Jun 12, 2023. Accepted for publication Nov 17, 2023. Published online Nov 28, 2023.
doi: 10.21037/tlcr-23-383
View this article at: https://dx.doi.org/10.21037/tlcr-23-383

Introduction

Targeted therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective for treating non-small cell lung cancer (NSCLC) harboring activating mutations in the *EGFR* gene (1). The frequency of *EGFR* mutations varies according to ethnicity and is higher in Asians than in Western populations. In Asian patients with advanced NSCLC and adenocarcinoma histology, *EGFR* mutations are found in around half of all tumors. The most common *EGFR* mutations detected in NSCLC are exon 19 deletion (Del19) and a point mutation (L858R) in exon 21 (2,3).

Approved TKIs include first- (gefitinib, erlotinib), second- (afatinib, dacomitinib) and third- (osimertinib) generation agents. Although treatment with first-line gefitinib, erlotinib and afatinib is the standard of care for *EGFR* mutation-positive NSCLC, resistance inevitably develops, commonly due to secondary acquisition of the T790M *EGFR* mutation. The third-generation *EGFR* TKI, osimertinib is effective against *EGFR* T790M-positive NSCLC (1). In Korea, osimertinib is not reimbursable currently for first-line treatment and is used as second-line therapy.

In clinical trials, first-line afatinib has consistently shown efficacy with good tolerability in patients with *EGFR* mutation-positive NSCLC (4-8). Real-world studies have also demonstrated the effectiveness and tolerability of first-line afatinib in these patients (9-11). A single-center retrospective analysis of Korean patients reported that first-line afatinib had superior progression-free survival (PFS) compared to gefitinib or erlotinib (10). In a multicenter real-world study of Korean patients with *EGFR* mutation-positive NSCLC, initial analysis showed that first-line afatinib was well tolerated with no new safety signals and effectiveness results were encouraging including in patients with baseline brain metastases and/or uncommon *EGFR* mutations (11). At the time of the previous analysis (data cut-off 4 April 2019), survival data were not mature. Here, we briefly present updated effectiveness results including PFS and overall survival (OS). We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/rc).

Highlight box

Key findings

- First-line afatinib was an effective treatment in patients with advanced epidermal growth factor receptor (*EGFR*) mutation positive non-small cell lung cancer (NSCLC). The median progression-free survival (PFS) was 20.2 months and overall survival (OS) was 48.6 months.

What is known and what is new?

- Afatinib has been shown to be efficacious with good tolerability in clinical trials. Previously, interim analysis of the current retrospective multicenter reported encouraging effectiveness data and a favorable safety profile.
- The current report provided an updated result with the mature OS data. In addition, presence of baseline brain metastases was identified to reduce median PFS, while OS was found to be longer in patients with common *EGFR* mutations. Afatinib was also observed to be similarly effective regardless of patient age.

What is the implication, and what should change now?

- First-line afatinib is an effective treatment strategy for Korean patients with *EGFR* mutation-positive NSCLC, especially in the subset harboring common *EGFR* mutations. Favorable OS is observed with afatinib alone without any specific brain treatment in patients with brain metastasis, indicates the utility of afatinib in the treatment of brain metastasis patients.

Methods

Patient population

Details of the study have been published previously (11). Briefly, this was a retrospective, multicenter (15 sites across South Korea) review of electronic records of adult patients (aged >20 years) with advanced *EGFR* mutation-positive NSCLC enrolled in the Korean Academy of Tuberculosis and Respiratory Disease (KATRD) *EGFR* cohort who had initiated first-line afatinib between April 2007 and December 2018 (11). Patient subgroups included the presence or absence of baseline brain metastases, afatinib dose reduction, baseline *EGFR* mutation type, age group, and treatments received.

Statistical analysis

Outcomes were PFS and OS evaluated using Kaplan-Meier survival curves. PFS was defined as the time from initiation of afatinib to objective tumor progression or all-cause death according to RECIST 1.1 criteria. OS was defined as the time from the first dose of afatinib until death. PFS and OS were censored using a data cut-off date of 31 August 2021. A log-rank test and Cox proportional hazards model were used to compare patient subgroups. Statistical analyses were performed using SAS version 9.4. A P value of <0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the guidelines of the Helsinki Declaration (as revised in 2013). The study was approved by the institutional ethics review boards of: Korea University Guro Hospital (No. 2018GR0013), Asan Medical Center (No. 2018-0012), Yonsei University Gangnam Severance Hospital (No. 3-2020-0003), Konkuk University Medical Center (No. KUH1010909), Catholic University Seoul St. Mary's Hospital (No. KC20RCDI0129), Wonkwang University Hospital (No. WKUH-201606-HR-058), Inha University Hospital Institutional Review Board (No. 2020-01-016), Chungnam National University Institutional Review Board (No. CNUH 2020-02-022-006), Kyungpook National University Chilgok Hospital Institutional Review Board (No. KNUCH 2020-01-010), Hallym University Sacred Heart Hospital Institutional Review Board (No. HALLYM 2020-07-041), Chonnam National University Hwasun Hospital Institutional Review Board (No. CNUHH-2017-179), Daegu Catholic University Medical Center Institutional Review Board (No. CR-18-097), Institutional Review Board of Severance Hospital (No. 4-2019-1214), Pusan National University Yangsan Hospital Institutional Review Board (No. 05-2020-006), and Kosin University Gospel Hospital Institutional Review Board (No. KUGH 2017-11-030). Individual consent for this retrospective analysis was waived.

Results

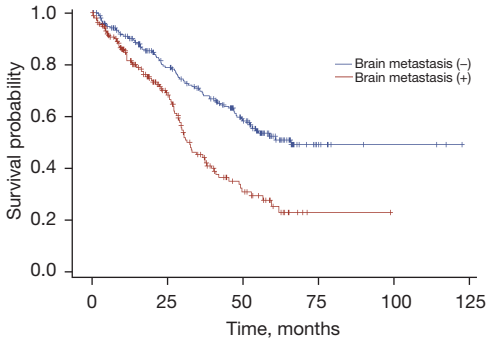
As reported previously (11), most patients in the KATRD *EGFR* cohort treated with first-line afatinib (N=422) were male (54.3%), never smokers (52.1%), with stage IVA/B disease (91.9%), adenocarcinoma (95.3%), Eastern Cooperative Oncology Group (ECOG) performance status <2 (72.5%), and received the approved afatinib starting dose (40 mg, once daily; 82.9%). The most received treatment following progression to afatinib was cytotoxic chemotherapy (71.6%) followed by 3rd generation TKIs (16.7%) (Table S1). Overall, 39.8% had baseline brain metastases, and common baseline *EGFR* mutations detected were Del19 (59.0%) and L858R (25.1%) (11).

Kaplan-Meier analyses of the cohort (n=421) showed that median PFS was 20.2 months [95% confidence interval (CI): 17.5–24.5] and median OS was 48.6 months (95% CI: 40.8–56.4). OS rates at 36 and 60 months were 60.1% and 42.3%, respectively.

Subgroup analyses showed that the presence *vs.* absence of baseline brain metastases was associated with significantly reduced median PFS (14.9 *vs.* 28.0 months; P<0.001) and median OS (32.2 *vs.* 65.6 months; P<0.001). *Figure 1* shows Kaplan-Meier survival curves for OS in patients with/without brain metastases. Comparative OS rates at 36 and 60 months in patients with or without brain metastases were 45.4% *vs.* 70.0% and 25.8% *vs.* 52.5%, respectively.

Among patients with brain metastasis, 41.4% were not receiving treatment during initial lung cancer diagnosis (Table S2). Among patients who were not receiving treatment, the objective response rate of 0.712 (0% complete response, 71.2% partial response, 17.3% stable disease, and 11.5% progressive disease). There was no statistically significant difference between patients with brain metastasis who received *vs.* did not receive brain metastasis treatment in terms of PFS (14.5 *vs.* 14.4 months; P=0.683) and OS (30.6 *vs.* 40.9 months; P=0.220) (Figures S1,S2).

The presence of common baseline *EGFR* mutations (Del19, L858R) was associated with significantly prolonged



Subgroups	No. of events/no. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)
BM+	91/189	32.2 (28.7–37.9)	45.4	25.8
BM–	86/232	65.6 (51.9–NR)	70.0	52.5

Figure 1 Kaplan-Meier overall survival curves in patients with (BM+) or without (BM–) baseline brain metastases. BM, brain metastasis; CI, confidence interval; OS, overall survival; NR, not reached.

OS (49.6 *vs.* 30.1 months; P=0.017). Comparative OS rates at 36 and 60 months in patients with or without common *EGFR* mutations were 61.3% *vs.* 43.4% and 44.0% *vs.* 20.6%, respectively. Individually, a statistically significant increase in PFS was seen in patients with Del19 (20.8 *vs.* 15.6 months; P=0.009) while statistically significant lower PFS was seen in patients with L858R (15.6 *vs.* 19.9 months; P=0.017) (Figures S3,S4). However, no statistical differences in OS were seen when comparing the presence *vs.* absence of Del19 (P=0.432) and L858R (P=0.553) (Figures S5,S6).

The presence of acquired *EGFR* T790M mutation was associated with significantly reduced median PFS (18.6 *vs.* 21.9 months; P=0.0005), but there were no significant differences in median OS between T790M+ and T790M– groups (52.5 *vs.* 48.6 months; P=0.263). There were no significant differences in OS based on the presence or absence of exon 18 mutations (G719A, G719C, G719S) (P=0.315; Figure S7) or exon 20 mutation S768I (P=0.503; Figure S8).

There were no significant differences in PFS or OS for patients stratified by afatinib dose reduction or by age group (<70/≥70 years) (*Table 1*). Lastly, there was also no significant difference in OS based on treatment received after progression to afatinib (P=0.239; Figure S9).

Discussion

A previous publication on the effectiveness of first-line afatinib in the KATRD *EGFR* cohort of patients with advanced *EGFR* mutation-positive NSCLC (data cut-off 4 April 2019) reported median time-to-treatment discontinuation (TTD) of 17.8 months and an overall response rate of 62.6%. Afatinib was well-tolerated and treatment-related adverse events (mainly diarrhea and rash) were managed effectively with dose reductions (11). Here, we provide an update on the previous analysis and provide additional insight into the effectiveness of first-line afatinib on subgroups of patients based on brain metastasis and baseline *EGRF* mutations.

In this brief updated analysis, median PFS was 20.2 months and median OS was 48.6 months. Median OS was superior to that reported in other real-world clinical studies of *EGFR* mutation-positive NSCLC patients. Two global studies of patients treated with sequential afatinib and osimertinib reported median OS of 37.6 months (12) and 36.5 months (13) and median OS was longer in Asian patient subgroups in both studies (44.8 and 42.3 months, respectively). Chart review of Japanese patients treated with afatinib reported a median OS of 38.6 months (14). In two retrospective Taiwanese studies, median OS was 39.1 months in patients treated with afatinib (15) and 37.0 months in patients who received first-line gefitinib, afatinib or erlotinib (16). The median PFS observed in this study was almost twice longer than that reported in pooled analyses of patients with uncommon *EGFR* mutations (11 months) (17) and in EGFR-TKI-naïve patients (13 months) (18). However, recent prospective trials and real-world studies conducted in Japan and Korea reported similar PFS of 16–20 months (7,19,20). Thus, first-line Afatinib followed by a second-line osimertinib may present a new treatment strategy for a specific subset of patients who are prone to developing T790M as a resistance mechanism. This is supported by a recently published data from the retrospective "Totality outcome of afatinib sequential treatment in patients with *EGFR* mutation-positive non-small cell lung cancer in South Korea (TOAST)" study showed that first-line afatinib treatment with various second-line treatments, including osimertinib, is an effective therapeutic strategy for *EGFR* mutation-positive NSCLC patients (21). The median PFS observed in this study was also comparable to the PFS of the combination therapy of erlotinib with ramucirumab, an anti-VEGF-R2 antibody, among patients with *EGFR*-mutated advanced NSCLC (22). However, the trial reported higher incidence rates of grade ≥3 adverse events than reported for afatinib in our previous publication (11). Further, a large real-world comparison study of TKIs in Europe reported statistically significant PFS and 1-year OS of afatinib

Table 1 PFS and OS in the cohort and subgroups

Subgroups	PFS		OS	
	Median (95% CI) (months)	P value	Median (95% CI) (months)	P value
Overall (N=421)	20.2 (17.5–24.5)	–	48.6 (40.7–56.4)	–
BM status		<0.001		<0.001
BM+ (n=189)	14.9 (13.0–17.4)		32.2 (28.7–37.9)	
BM– (n=232)	28.0 (21.9–36.7)		65.6 (51.9–NR)	
EGFR mutation type		0.546		0.017
Common* (n=392)	20.6 (18.1–25.1)		49.6 (41.1–60.6)	
Uncommon (n=29)	13.8 (5.5–48.6)		30.1 (9.5–59.3)	
Dose reduction		0.513		0.189
Yes (n=253)	20.9 (17.6–26.5)		52.8 (41.1–65.6)	
No (n=168)	18.7 (14.6–25.8)		41.8 (31.2–51.9)	
Age group		0.1099		0.725
<70 years (n=273)	19.1 (16.4–23.9)		49.1 (40.4–58.6)	
≥70 years (n=148)	23.2 (17.2–36.4)		47.8 (34.0–NR)	
EGFR mutation†		0.0005		0.263
T790M+ (n=100)	18.6 (15.1–21.4)		52.5 (42.4–65.6)	
T790M– (n=321)	21.9 (17.4–29.0)		48.6 (36.6–NR)	

P values were calculated by log-rank tests. *, common *EGFR* mutations were Del19 and L858R and present in 59.0% and 25.1% of patients, respectively (11); †, treated with sequential afatinib and osimertinib (n=21) or afatinib and chemotherapy (n=89) (11). PFS, progression-free survival; OS, overall survival; CI, confidence interval; BM, brain metastases; NR, not reached; EGFR, epidermal growth factor receptor.

compared with erlotinib and gefitinib (23). These results support the real-world effectiveness and safety of afatinib.

Baseline brain metastases, which were present in nearly 40% of patients, were associated with significantly reduced PFS and OS. However, there was no statistically significant difference in PFS and OS between patients who received additional treatment for their brain metastasis compared with those who did not. Common baseline *EGFR* mutations (Del19, L858R) were also associated with significantly prolonged median OS. When analyzed separately, Del19 mutation was associated with increased PFS but L858R mutation was associated with lower PFS. Association of the presence of the Del19 mutation at baseline (but not the L858R mutation) with prolonged OS was previously reported in patients treated with sequential afatinib and osimertinib with increases in median OS by 4 months (12) and 1.5 months (13). Thus, it is likely that first-line Afatinib to be beneficial in patients with baseline Del19 mutation.

A retrospective South Korean study which categorized uncommon *EGFR* mutations (n=64) according to their incidence showed that first-line afatinib was effective in patients with NSCLC harboring "major uncommon" (G719X and L861Q), and compound *EGFR* mutations. Median OS was 30.6 and 29.1 months, respectively. However, survival in patients with "minor uncommon" mutations (exon 20 insertion, S768I, and *de novo* T790M) was reduced: median OS was 8.5 months (24). We did not observe statistically significant differences in OS based on the presence of uncommon mutations in Exon 18 (G719A, G719C, G719S) or exon 20 (S768I).

No significant differences in survival were found between patients stratified by the presence/ absence of T790M *EGFR* mutation treated with afatinib and subsequent therapy with osimertinib/chemotherapy. Sequential afatinib and osimertinib is known to be superior to sequential afatinib and chemotherapy for NSCLC harboring a T790M

mutation (25).

Afatinib was effective in elderly patients ≥70 years of age and supports results from the Japanese phase 2 trial of *EGFR* mutation-positive patients aged ≥75 years with advanced NSCLC who achieved a median OS of 35.2 months (26), subgroup analyses of older patients (≥65 and ≥75 years) in the LUX-Lung 3, 6 and 7 clinical trials (27), and results from the GIDEON prospective non-interventional study demonstrating higher median PFS in patients ≥70 years (28). Effectiveness of afatinib was also shown in patients who had the dose reduced to 20 or 30 mg. Systematic review of six studies which compared 30 mg with 40 mg doses of afatinib concluded that effectiveness, as evaluated by PFS, appeared to be similar in patients who had no brain metastasis (29). The GIDEON study also reported comparable effectiveness of starting dose of <40 and 40 mg (30). These results suggest first-line afatinib to be an effective treatment option in elderly patients with an option for dose adjustment.

As noted in the previous publication which reported primary analyses from the KATRD cohort (11), study limitations mainly relate to the retrospective study design. Nevertheless, our study represents real-world clinical practice and provides useful insights regarding the use of first-line afatinib for the treatment of advanced *EGFR* mutation-positive NSCLC in Korea. Assessment of PFS in this study was conducted by the investigators rather than by blinded independent central reviewers, which may contribute to the slightly longer PFS observed in this study.

Conclusions

In conclusion, afatinib was effective in Korean patients with *EGFR* mutation-positive NSCLC with a median OS of over 4 years. The presence of baseline brain metastases and/or uncommon *EGFR* mutations were associated with reduced survival. In the absence of baseline brain metastases, median OS was more than 5 years.

Acknowledgments

Under the direction of the authors, medical writing and editorial assistance was provided by Robert A. Furlong PhD and David P. Figgitt PhD, ISMPP CMPP™, Content Ed Net, with funding from Boehringer Ingelheim. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/coif). Y.S.C. declares being a stockholder in BicBio; Y.C.K. has received grants from AstraZeneca and honoraria from AstraZeneca, Merck Sharp & Dohme, Roche, Novartis, Janssen, Amgen, Ono Pharma, Bristol Myers Squibb, and Takeda; I.J.O. has received grants from AstraZeneca and Roche, personal fees from Gencurix, Janssen, Merck Sharp & Dohme, Ono Pharma, Panagene, Pfizer, Roche, and Yuhan, and honoraria from Amgen, AstraZeneca, Eli Lilly, Janssen, Menarini, Merck Sharp & Dohme, Novartis, Pfizer, and Yuhan; S.Y.L. has received honoraria from Boehringer Ingelheim; T.W.J. has received honoraria from Boehringer Ingelheim. The other authors have no conflicts of interest to disclose.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the guidelines of the Helsinki Declaration (as revised in 2013). The study was approved by the institutional ethics review boards of Korea University Guro Hospital (No. 2018GR0013), Asan Medical Center (No. 2018-0012), Yonsei University Gangnam Severance Hospital (No. 3-2020-0003), Konkuk University Medical Center (No. KUH1010909), Catholic University Seoul St. Mary's Hospital (No. KC20RCDI0129), Wonkwang University Hospital (No. WKUH-201606-HR-058), and Inha University Hospital Institutional Review Board (No. 2020-01-016), Chungnam National University Institutional Review Board (No. CNUH 2020-02-022-006), Kyungpook National University Chilgok Hospital Institutional Review Board (No. KNUCH 2020-01-010), Hallym University Sacred Heart Hospital Institutional Review Board (No. HALLYM 2020-07-041), Chonnam National University

Hwasun Hospital Institutional Review Board (No. CNUHH-2017-179), Daegu Catholic University Medical Center Institutional Review Board (No. CR-18-097), Institutional Review Board of Severance Hospital (No. 4-2019-1214), Pusan National University Yangsan Hospital Institutional Review Board (No. 05-2020-006), and Kosin University Gospel Hospital Institutional Review Board (No. KUGH 2017-11-030). Individual consent for this retrospective analysis was waived.

References

1. Girard N. Optimizing outcomes in EGFR mutation-positive NSCLC: which tyrosine kinase inhibitor and when? Future Oncol 2018;14:1117-32.
2. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
3. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67.
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
5. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.
6. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17:577-89.
7. Park K, Kim JS, Kim JH, et al. An open-label expanded access program of afatinib in EGFR tyrosine kinase inhibitor-naïve patients with locally advanced or metastatic non-small cell lung cancer harboring EGFR mutations. BMC Cancer 2021;21:802.
8. de Marinis F, Laktionov KK, Poltoratskiy A, et al. Afatinib in EGFR TKI-naïve patients with locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer: Interim analysis of a Phase 3b study. Lung Cancer 2021;152:127-34.
9. Park K, Wan-Teck Lim D, Okamoto I, et al. First-line afatinib for the treatment of EGFR mutation-positive non-small-cell lung cancer in the 'real-world' clinical setting. Ther Adv Med Oncol 2019;11:1758835919836374.
10. Kim Y, Lee SH, Ahn JS, et al. Efficacy and Safety of Afatinib for EGFR-mutant Non-small Cell Lung Cancer, Compared with Gefitinib or Erlotinib. Cancer Res Treat 2019;51:502-9.
11. Lee SY, Choi CM, Chang YS, et al. Real-world experience of afatinib as first-line therapy for advanced EGFR mutation-positive non-small cell lung cancer in Korea. Transl Lung Cancer Res 2021;10:4353-67.
12. Hochmair MJ, Morabito A, Hao D, et al. Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: final analysis of the GioTag study. Future Oncol 2020;16:2799-808.
13. Popat S, Jung HA, Lee SY, et al. Sequential afatinib and osimertinib in patients with EGFR mutation-positive NSCLC and acquired T790M: A global non-interventional study (UpSwinG). Lung Cancer 2021;162:9-15.
14. Ito K, Murotani K, Kubo A, et al. Propensity score analysis of overall survival between first- and second-generation EGFR-TKIs using real-world data. Cancer Sci 2020;111:3705-13.
15. Su PL, Wu YL, Chang WY, 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.
16. Lin YT, Chen JS, Liao WY, et al. Clinical outcomes and secondary epidermal growth factor receptor (EGFR) T790M mutation among first-line gefitinib, erlotinib and afatinib-treated non-small cell lung cancer patients with activating EGFR mutations. Int J Cancer 2019;144:2887-96.
17. Wang C, Zhao K, Hu S, et al. Clinical Outcomes of Afatinib Versus Osimertinib in Patients With Non-Small Cell Lung Cancer With Uncommon EGFR Mutations: A Pooled Analysis. Oncologist 2023;28:e397-405.

18. Passaro A, de Marinis F, Tu HY, et al. Afatinib in EGFR TKI-Naïve Patients with Locally Advanced or Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Pooled Analysis of Three Phase IIIb Studies. Front Oncol 2021;11:709877.
19. Takata S, Morikawa K, Tanaka H, et al. Prospective exosome-focused translational research for afatinib (EXTRA) study of patients with nonsmall cell lung cancer harboring EGFR mutation: an observational clinical study. Ther Adv Med Oncol 2023;15:17588359231177021.
20. Ninomiya T, Ishikawa N, Kozuki T, et al. A randomized phase II study of afatinib alone or combined with bevacizumab for treating chemo-naïve patients with non-small cell lung cancer harboring EGFR mutations. Lung Cancer 2023;184:107349.
21. Jung HA, Hong MH, Lee HW, et al. Totality outcome of afatinib sequential treatment in patients with EGFR mutation-positive non-small cell lung cancer in South Korea (TOAST): Korean Cancer Study Group (KCSG) LU-19-22. Transl Lung Cancer Res 2022;11:1369-79.
22. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:1655-69.
23. Pluzanski A, Krzakowski M, Kowalski D, et al. Real-world clinical outcomes of first-generation and second-generation epidermal growth factor receptor tyrosine kinase inhibitors in a large cohort of European non-small-cell lung cancer patients. ESMO Open 2020;5:e001011.
24. Kim MH, Choi CM, Lee SY, et al. First-line Afatinib in Patients With Non-small-cell Lung Cancer With Uncommon EGFR Mutations in South Korea. Anticancer Res 2022;42:1615-22.
25. Chen CH, Chang JW, Chang CF, et al. Real-world Afatinib Outcomes in Advanced Non-small Cell Lung Cancer Harboring EGFR Mutations. Anticancer Res 2022;42:2145-57.
26. Minegishi Y, Yamaguchi O, Sugawara S, et al. A phase II study of first-line afatinib for patients aged ≥75 years with EGFR mutation-positive advanced non-small cell lung cancer: North East Japan Study Group trial NEJ027. BMC Cancer 2021;21:208.
27. Wu YL, Sequist LV, Tan EH, et al. Afatinib as First-line Treatment of Older Patients With EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 Trials. Clin Lung Cancer 2018;19:e465-79.
28. Brueckl WM, Reck M, Schäfer H, et al. Older patients with EGFR mutation-positive non-small cell lung cancer treated with afatinib in clinical practice: A subset analysis of the non-interventional GIDEON study. J Geriatr Oncol 2023;14:101394.
29. Wang Z, Du X, Chen K, et al. Impact of Dose Reduction of Afatinib Used in Patients With Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Front Pharmacol 2021;12:781084.
30. Brückl WM, Reck M, Griesinger F, et al. Afatinib as first-line treatment in patients with EGFR-mutated non-small cell lung cancer in routine clinical practice. Ther Adv Med Oncol 2021;13:17588359211012361.

Cite this article as: Choi J, Choi CM, Chang YS, Lee KY, Kim SJ, Yang SH, Ryu JS, Lee JE, Lee SY, Park JY, Kim YC, Oh IJ, Jung CY, Lee SH, Yoon SH, Lee SY, Jang TW. Real-world first-line afatinib for advanced *EGFR* mutation-positive non-small cell lung cancer in Korea: updated survival data. Transl Lung Cancer Res 2023;12(11):2275-2282. doi: 10.21037/tlcr-23-383

Supplementary

Table S1 Treatment received following PD

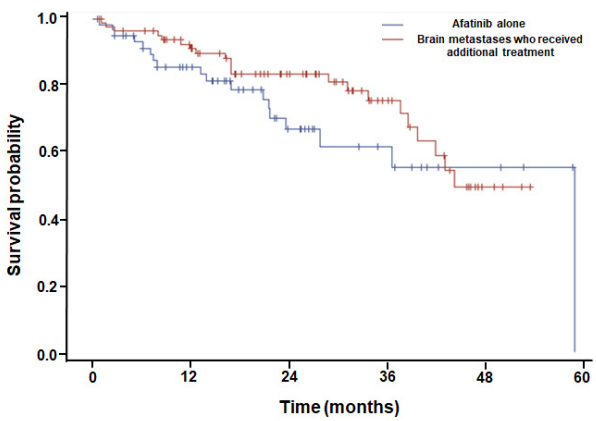
Treatment following PD	N	%
Cytotoxic chemotherapy	90	71.4
Gefitinib, erlotinib	9	7.1
3rd generation EGFR TKI	21	16.7
ALK TKI	1	0.8
IND	5	4.0

PD, progressive disease; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; IND, investigational new drug.

Table S2 Treatment of patients with brain metastasis at time of initial lung cancer diagnosis and their afatinib treatment duration

Brain metastasis treatment	N (%)	Afatinib treatment duration (start to end of administration)	
		Mean (SD)	Median [Q1, Q3]
No treatment	60 (41.4)	324.6 (247.4)	308 [125, 464]
Surgery	7 (4.8)	452.1 (300.4)	430 [261, 752]
GKRS	21 (14.5)	457.9 (292.2)	435 [231, 614]
CyberKife	4 (2.8)	259.8 (136.1)	209.5 [168, 351.5]
WBRT	51 (35.1)	290.1 (188.1)	258 [167, 376]
SRS	2 (1.4)	178.0 (8.5)	178 [172, 184]

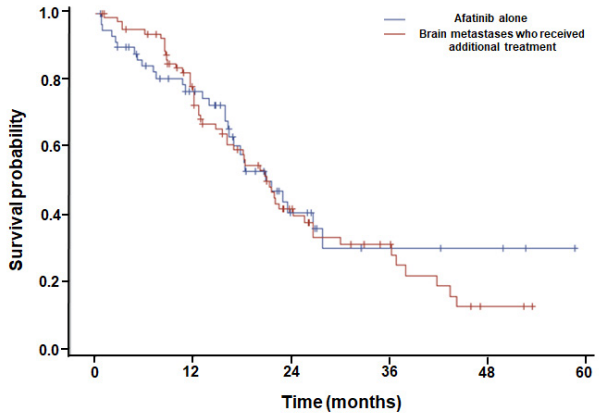
GKRS, gamma knife radiosurgery; WBRT, whole brain radiation therapy; SRS, stereotactic surgery; SD, standard deviation; Q1, 25th percentile; Q3, 75th percentile.



Subgroup	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
Treated	85	30.6 (27.5–NR)	49.6	49.6	0.220
Not treated	60	40.9 (19.2–40.9)	55.6	0	

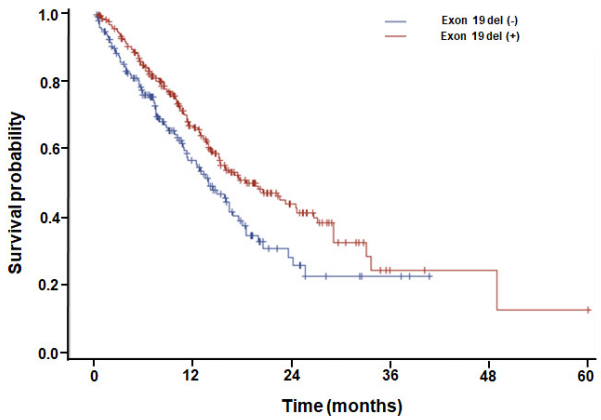
Figure S1 Kaplan-Meier OS curves in patients with baseline brain metastases who received additional treatment *vs.* afatinib alone. CI, confidence interval; OS, overall survival; mo, months.

https://dx.doi.org/10.21037/tlcr-23-383



Subgroup	No of patients	Median PFS (95% CI) (months)	36-mo PFS rate (%)	60-mo PFS rate (%)	P value
Treated	85	14.5 (11.2–17.8)	12.4	12.4	0.683
Not treated	60	14.4 (11.4–19.2)	29.9	29.9	

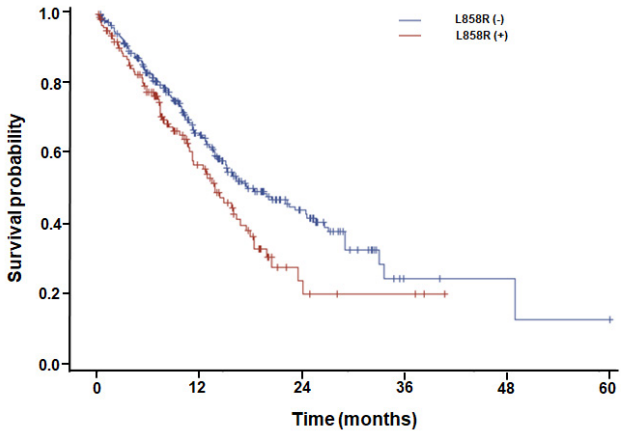
Figure S2 Kaplan-Meier PFS curves in patients with baseline brain metastases who received additional treatment *vs*. afatinib alone. PFS, progression-free survival; CI, confidence interval; mo, months.



Mutations	No. of patients	Median PFS (95% CI) (months)	36-mo PFS rate (%)	60-mo PFS rate (%)	P value
Del19	252	20.8 (17.1–27.8)	32.1	12.0	0.009
Others	163	15.6 (12.6–19.0)	22.2	22.2	

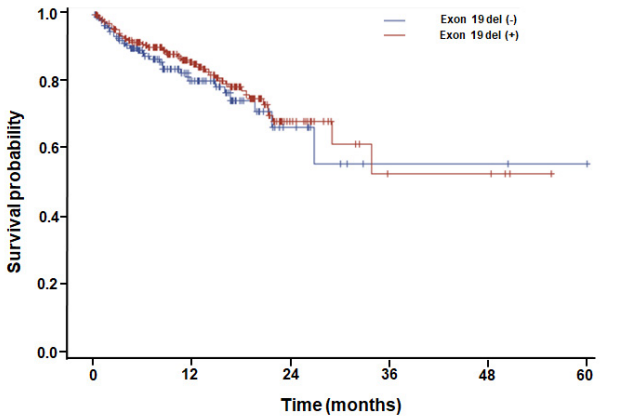
Figure S3 Kaplan-Meier PFS curves in patients with Del19 mutation *vs*. without. PFS, progression-free survival; CI, confidence interval; mo, months.

https://dx.doi.org/10.21037/tlcr-23-383



Mutations	No. of patients	Median PFS (95% CI) (months)	36-mo PFS rate (%)	60-mo PFS rate (%)	P value
L858R	129	15.6 (12.6–19.0)	19.4	19.4	0.017
Others	286	19.9 (17.1–27.7)	32.0	12.0	

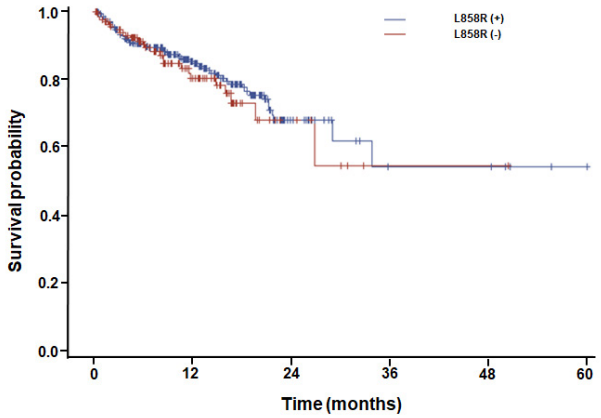
Figure S4 Kaplan-Meier PFS curves in patients with *vs.* without L858R mutation. PFS, progression-free survival; CI, confidence interval; mo, months.



Mutations	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
Del19	256	NR (40.9–NR)	68.1	52.5	0.432
Others	161	NR (37.7–NR)	66.4	55.4	

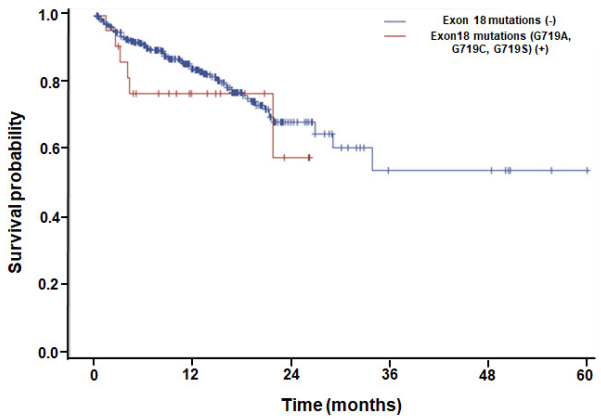
Figure S5 Kaplan-Meier OS curves in patients with Del19 mutation *vs.* without. OS, overall survival; CI, confidence interval; mo, months; NR, not reached.

https://dx.doi.org/10.21037/tlcr-23-383



Mutations	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
L858R	137	NR (37.7–NR)	68.0%	54.4%	0.553
Others	280	NR (40.9–NR)	67.7%	53.9%	

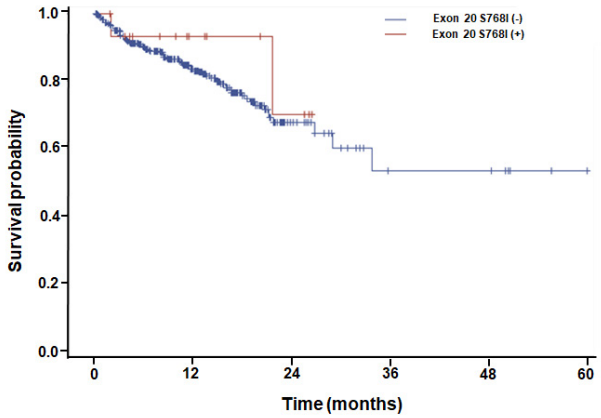
Figure S6 Kaplan-Meier OS curves in patients with *vs.* without L858R mutation. OS, overall survival; CI, confidence interval; mo, months; NR, not reached.



Mutations	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
Exon 18 mutations (G719A, G719C, G719S)	22	NR (30.5–NR)	57.4	57.4	0.315
Others	395	NR (40.9–NR)	68.1	53.7	

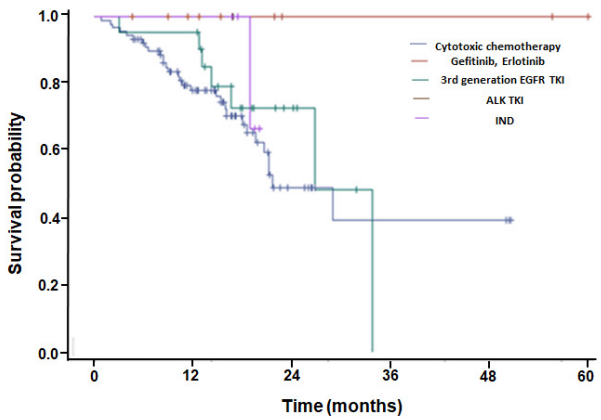
Figure S7 Kaplan-Meier OS curves in patients according to the presence or absence of Exon18 mutations (G719A, G719C, G719S). OS, overall survival; CI, confidence interval; mo, months; NR, not reached.

https://dx.doi.org/10.21037/tlcr-23-383



Mutations	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
Exon 20 (S768I)	16	NR (30.5–NR)	70.0	70.0	0.503
Others	401	NR (40.9–NR)	67.6	53.3	

Figure S8 Kaplan-Meier OS curves in patients according to the presence or absence of exon 20 S768I. OS, overall survival; CI, confidence interval; mo, months; NR, not reached.



Treatments	No. of patients	Median OS (95% CI) (months)	36-mo OS rate (%)	60-mo OS rate (%)	P value
Cytotoxic chemotherapy	90	20.5 (27.5–NR)	49.1	39.3	0.239
Gefitinib, Erlotinib	9	NR (NR–NR)	100	100	
3rd generation EGFR TKI	21	37.7 (23.4–47.6)	72.7		
ALK TKI	1	NR (NR–NR)	100	100	
IND	5	NR (NR–NR)	66.7	66.7	

Figure S9 Kaplan-Meier curves OS in patients according to treatment received after PD. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; ALK, anaplastic lymphoma kinase; IND, investigational new drug; OS, overall survival; CI, confidence interval; mo, months; NR, not reached; PD, progressive disease.

https://dx.doi.org/10.21037/tlcr-23-383