Original Article

Real-world analysis of first-line afatinib in patients with *EGFR*-mutant non-small cell lung cancer and brain metastasis: survival and prognostic factors

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Background: Overall survival (OS) in patients with non-small cell lung cancer (NSCLC) and brain metastases (BMs) is poor. We aimed to identify prognostic factors and ascertain treatment outcomes of first-line afatinib for patients with epidermal growth factor receptor (EGFR)-mutant NSCLC with BM in a real-world setting.

Methods: This retrospective observational study reviewed electronic records of patients with *EGFR*-mutant NSCLC who received first-line afatinib treatment between October 2014 and October 2019 in 16 hospitals across South Korea. The Kaplan-Meier method estimated time on treatment (TOT) and OS; multivariate analyses were performed using Cox proportional hazards (PH) models.

Results: Among 703 patients who received first-line afatinib, 262 (37.3%) had baseline BM. Of 441 patients without baseline BM, 92 (20.9%) developed central nervous system (CNS) failure. Compared with patients without CNS failure, those with CNS failure during afatinib treatment were younger (P=0.012), had a higher Eastern Cooperative Oncology Group (ECOG) performance status (PS) (P<0.001), increased metastatic site involvement (P<0.001), advanced stage disease (P<0.001), with liver metastasis (P=0.008) and/or bone metastasis (P<0.001) at baseline. Cumulative incidence of CNS failure in years 1, 2 and 3 was 10.1%, 21.5% and 30.0%, respectively. In multivariate analysis, cumulative incidence was significantly higher in patients with ECOG PS ≥2 (P<0.001), uncommon *EGFR* mutations (P=0.001), and no baseline pleural metastasis (P=0.017). Median TOT was 16.0 months (95% CI: 14.8–17.2) and, in patients with CNS failure, without CNS failure, and with baseline BM was 12.2, 18.9, and 14.1 months, respectively (P<0.001). Median OS was 52.9 months (95% CI: 45.4–60.3) and, in patients with CNS failure, without CNS failure, and with

baseline BM was 29.1, 67.3 and 48.5 months, respectively (P<0.001).

Conclusions: First-line afatinib in the real-world setting showed clinically meaningful effectiveness in patients with *EGFR*-mutant NSCLC and BM. CNS failure was a poor prognostic factor for TOT and OS correlating with younger age, poor ECOG PS, higher metastatic number, advanced disease stage, uncommon *EGFR* mutations, and baseline liver and/or bone metastases.

Keywords: Afatinib; non-small cell lung cancer (NSCLC); brain metastasis (BM); EGFR mutation; tyrosine kinase inhibitor (TKI)

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Introduction

In 2020, lung cancer was the second most commonly diagnosed cancer globally (behind female breast cancer), with more than 2.2 million new cases diagnosed and accounting for nearly 1.8 million deaths (1). Projections estimated that, during 2021 in Korea, more than 32,000 incident cancer cases and nearly 19,000 cancer deaths due to lung cancer would occur (2). Over the past two decades, 5-year relative survival rates in Korea have improved from 11.3% [1993–1995] to 30.2% [2013–2017], which is probably due to improvements in diagnosis and therapy (3). However, over 40% of patients with non-small cell lung cancer (NSCLC) present with stage IV disease (4).

Highlight box

Key findings

- First-line afatinib in the real-world setting showed clinically meaningful effectiveness in patients with epidermal growth factor receptor (*EGFR*)-mutant non-small-cell lung cancer (NSCLC) and brain metastases.
- CNS failure was a poor prognostic factor for time in treatment and overall survival (OS) correlating with younger age, poor ECOG performance status, higher metastatic number, advanced disease stage, uncommon *EGFR* mutations, and baseline liver and/or bone metastases.

What is known and what is new?

- OS in patients with NSCLC and brain metastases is poor.
- We identified prognostic factors and ascertained treatment outcomes of first-line afatinib for patients with *EGFR*-mutant NSCLC with brain metastases in a real-world setting.

What is the implication, and what should change now?

- Our findings confirm that first-line afatinib in the real-world setting has clinically meaningful effectiveness in patients with EGFR-mutant NSCLC and brain metastases. Prognostic factors identified may support treatment decisions.

Targeted therapy based on establishing molecularly distinct driver mutations for NSCLC has increased treatment options and improved clinical outcomes. Targeted agents include tyrosine kinase inhibitors (TKIs), gefitinib, erlotinib, afatinib and osimertinib, which target mutations in epidermal growth factor receptor (EGFR) and the multitarget TKI, crizotinib, for anaplastic lymphoma kinase (ALK)-positive or ROS1-positive NSCLC (5,6). *EGFR* mutation frequency varies according to ethnicity and, in Asian patients with advanced NSCLC and adenocarcinoma histology, *EGFR* mutations are found in approximately half of all tumors. The most common *EGFR* mutations are deletion of exon 19 and a L858R point mutation in exon 21 (7).

Afatinib is a second-generation irreversible ErbB-family TKI which covalently binds to EGFR and HER2/ERBB2 (erb-b2 receptor tyrosine kinase 2). In randomized and open-label clinical trials, first-line afatinib has consistently shown clinical benefit with good tolerability in patients with NSCLC and *EGFR* mutations achieving median progression-free survival (PFS) of 11.0 to 17.0 months (8-13).

Analysis of large cancer databases in the USA estimated the incidence of brain metastases (BMs) in NSCLC and lung cancer as approximately 10% and 20%, respectively (14,15). Elsewhere, in a population-based cancer registry in The Netherlands (n=938), the estimated cumulative 5-year incidence of BMs in lung cancer was 16.3% (16) and a retrospective analysis of East Asian patients with NSCLC (n=1,127) reported that 23.2% developed BMs (17). Despite improvements in treatment, survival for many NSCLC patients with BMs is poor, ranging from 7 to 47 months (18).

BMs in patients with NSCLC are often accompanied by *EGFR* mutations (24–40%) or *ALK* gene

rearrangements at diagnosis (17,19,20) and in one study of NSCLC patients with BMs (n=381), the cumulative incidence of *EGFR* mutations increased over time from 24% at baseline to 34%, 47% and 53% at 1, 3 and 5 years, respectively (19).

Preclinical studies have shown that afatinib penetrates the mouse blood brain barrier (21,22) and, in clinical studies, afatinib is active in patients with central nervous system (CNS) lesions as illustrated following a *post hoc* analysis of the LUX-Lung 3 (8), LUX-Lung 6 (9) and LUX-Lung 7 (10) randomized controlled trials (23,24), and in a prospective multicenter study in patients with *EGFR* mutation-positive NSCLC with leptomeningeal carcinomatosis (25). The CNS activity of afatinib, including its intracranial objective response rate and PFS, as well as CNS failure rate, in patients with baseline BMs is supported by data from real-world studies (26-29). However, there are limited reports on CNS failure in patients without baseline BMs during afatinib treatment.

To evaluate the CNS failure rate particularly in patients without baseline BMs as well as effectiveness of first-line afatinib therapy within a large cohort, we conducted a national, multicenter retrospective study in Korean patients with *EGFR* mutation-positive NSCLC in the real-world setting. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-832/rc).

Methods

Study design

This non-interventional, retrospective observational study reviewed electronic records of patients with *EGFR*-mutant NSCLC who received first-line afatinib treatment between October 2014 and October 2019 in 16 hospitals across South Korea. No power calculations to determine sample size were required for the study, although the study aimed to include at least 700 eligible patients.

Objectives

The primary objective was to investigate the CNS failure rate of first-line afatinib in NSCLC patients with *EGFR* mutations in a real-world setting. Secondary objectives were to determine the time on treatment (TOT) of first-line treatment and to assess other real-world effects of afatinib on overall survival (OS).

Ethics and patient confidentiality

The study and protocol were approved by the Institutional Review Board of the Kosin University Gospel Hospital (IRB, KUGH No. 2019-07-038); the other 15 participating hospitals were also informed and agreed with the study. This non-interventional, retrospective chart review study was carried out in compliance with the protocol and principles laid down in the Declaration of Helsinki (as revised in 2013), in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice and the relevant sponsor's Standard Operating Procedures. Patient identification code numbers were used to ensure patient confidentiality. As this was a non-interventional, retrospective chart review study based on existing data in general practice, it did not require patient informed consent as per Korean regulations.

Inclusion and exclusion criteria

Patients aged >18 years treated with first-line afatinib for *EGFR* mutation-positive stage IIIB/IV NSCLC were included in the study. Main exclusion criteria were patients who received first-line drug(s) other than afatinib, and those with insufficient clinical data.

Treatment

Patients with *EGFR* mutation-positive NSCLC received afatinib therapy, 40, 30 or 20 mg per day, orally.

Endpoints

The primary endpoint was CNS failure rate which was defined as CNS progression, e.g., appearance of new brain or leptomeningeal lesions during afatinib treatment in patients without baseline BMs.

Secondary endpoints included TOT, defined as the length of time from first to last dates of afatinib administration, and OS. Response and progression were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (30) and tumor response was investigator-assessed.

Statistical analysis

Descriptive statistics for continuous variables were summarized by number, mean, standard deviation, 95%

confidence interval (CI), median and range. Categorical and ordinal variables were summarized by frequency and percentage. Chi-squared and Fisher's exact tests were used to evaluate differences between categorical variables.

TOT and OS were estimated using the Kaplan-Meier method, and the median plus 95% confidence intervals (CI) reported.

Cox proportional hazards (PH) models were used to investigate the effect of independent variables on survival outcomes. Variables with P<0.10 in the univariate Cox PH model were included in the multivariate Cox PH model.

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York), and R software version 4.0.3 for Windows (R Development Core Team).

Results

Of 703 eligible patients included in the study, 262 (37.3%) had baseline BMs. Baseline characteristics of patients with or without baseline BMs are summarized in *Table 1*. Compared with patients without BMs at baseline (n=441), the group of patients with baseline BMs (n=262) consisted of fewer males (45.4% *vs.* 54.9%, P=0.015), and had involvement of more metastatic sites (3–6 sites: 42.4% *vs.* 12.5%, P<0.001), advanced stage disease (stage IVB: 61.1% *vs.* 31.5%, P<0.001), increased bone metastatic rates (53.4% *vs.* 36.3%, P<0.001) and reduced pleural metastatic rates (25.6% *vs.* 43.3%, P<0.001). The most common *EGFR* mutations were exon 19 deletion (Del19) and L858R in both the without BM at baseline (58.7% and 31.3%, respectively) and with BM at baseline groups (56.1% and 35.5%, respectively). Uncommon *EGFR* mutations in patients with or without baseline BMs are summarized in Table S1.

Of 441 patients with no baseline BM, 92 (20.9%) developed BMs (CNS failure) during afatinib treatment. Compared with 349 patients without CNS failure, patients who developed CNS failure during treatment were younger (mean age: 60.9 *vs.* 64.2 years, P=0.012), had a higher ECOG performance status (PS) (≥2: 18.6% *vs.* 3.7%, P<0.001), more metastatic site involvement (3–6 sites: 32.6% *vs.* 7.2%, P<0.001), advanced stage disease (stage IVB: 51.1% *vs.* 26.4%, P<0.001), and baseline liver metastasis (15.2% *vs.* 6.6%, P=0.008) and/or bone metastasis (52.2% *vs.* 32.1%, P<0.001) (*Table 1*).

Median duration of CNS failure in patients receiving afatinib (n=92) was 12.2 months (95% CI: 9.9–14.6).

In patients without BM at baseline, the cumulative incidence of CNS failure in years 1, 2 and 3 was 10.1%, 21.5% and 30.0%, respectively. In univariate analysis, cumulative incidence was significantly higher in patients with ECOG PS ≥2 (P<0.001), compound or uncommon (i.e., not Del19 or L858R) *EGFR* mutations (P=0.022), stage IVB disease (P<0.001), liver metastasis (P=0.002), bone metastasis (P<0.001), and absence of pleural metastasis (P=0.036) (*Table 2*).

In multivariate analysis, the incidence of CNS failure was significantly higher in patients with ECOG PS ≥2 [hazard ratio (HR) = 5.98, 95% CI: 3.26–10.99; P<0.001], uncommon *EGFR* mutations (HR =3.07, 95% CI: 1.61–5.83; P=0.001), and no baseline pleural metastasis (HR =0.56, 95% CI: 0.35–0.90; P=0.017) (*Table 3*). These results are illustrated graphically in *Figure 1*.

Median TOT of afatinib in all patients was 16.0 months (95% CI: 14.8–17.2) and was significantly different (P<0.001) between patients with CNS failure (12.2 months, 95% CI: 9.9–14.6), without CNS failure (18.9 months, 95% CI: 16.8–21.0), and with baseline BM (14.1 months, 95% CI: 11.9–16.3) (Table S2; *Figure 2*). Significant within-category differences in TOT were found for ECOG PS (P=0.001), *EGFR* mutation status (P=0.049), number of metastatic organs (P<0.001), disease stage (P=0.008), baseline liver metastasis (P=0.001) and baseline bone metastasis (P=0.024) (Table S2).

Median OS in all patients was 52.9 months (95% CI: 45.4–60.3) and was significantly different (P<0.001) between patients with CNS failure (29.1 months, 95% CI: 23.3–35.0), without CNS failure (67.3 months, 95% CI: 43.7–90.9) and with baseline BM (48.5 months, 95% CI: not available) (Table S3; *Figure 2*). The between-group difference in OS at 10 months was significant (P=0.012). Significant within-category differences in OS were found for ECOG PS (P=0.016), *EGFR* mutation status (P<0.001), number of metastatic organs (P<0.001), disease stage (P=0.001), baseline liver metastasis (P<0.001) and baseline bone metastasis (P<0.001) (Table S3).

Discussion

This retrospective real-world study investigated the CNS failure rate of first-line afatinib in patients with *EGFR*-mutant NSCLC with or without BM. Reviews of patient electronic records revealed that, at baseline, BMs were identified in 37.3% of the whole cohort, and a further 20.9% of patients with no BMs at baseline developed CNS

Table 1 Baseline characteristics (N=703)

Parameter	No baseline brain metastases				Baseline brain metastases (n=262)	P
	Total (n=441)	New brain metastases (n=92)	No brain metastases (n=349)	P		
Age (years), mean (SD)	63.5 (11.2)	60.9 (10.3)	64.2 (11.3)	0.012	63.9 (11.0)	0.652
Sex, n (%)				0.909		0.015
Male	242 (54.9)	50 (54.3)	192 (55.0)		119 (45.4)	
Female	199 (45.1)	42 (45.7)	157 (45.0)		143 (54.6)	
Smoking status, n (%)				0.743		0.676
Never	281 (64.0)	57 (62.0)	224 (64.6)		173 (67.3)	
Former	119 (27.1)	25 (27.2)	94 (27.1)		63 (24.5)	
Current	39 (8.9)	10 (10.9)	29 (8.4)		21 (8.2)	
ECOG performance status, n (%)				<0.001		0.342
0–1	383 (93.2)	70 (81.4)	313 (96.3)		216 (91.1)	
≥2	28 (6.8)	16 (18.6)	12 (3.7)		21 (8.9)	
EGFR mutation, n (%)				0.305		0.468
Del19	259 (58.7)	53 (57.6)	206 (59.0)		147 (56.1)	
L858R	138 (31.3)	26 (28.3)	112 (32.1)		93 (35.5)	
Other	44 (10.0)	13 (14.1)	31 (8.9)		22 (8.4)	
No. of metastatic organs, n (%)				<0.001		<0.001
0–2	386 (87.5)	62 (67.4)	324 (92.8)		151 (57.6)	
3–6	55 (12.5)	30 (32.6)	25 (7.2)		111 (42.4)	
Stage (AJCC 8th edition), n (%)				<0.001		<0.001
3–4A	302 (68.5)	45 (48.9)	257 (73.6)		102 (38.9)	
4B	139 (31.5)	47 (51.1)	92 (26.4)		160 (61.1)	
Liver metastasis, n (%)	37 (8.4)	14 (15.2)	23 (6.6)	0.008	33 (12.6)	0.072
Bone metastasis, n (%)	160 (36.3)	48 (52.2)	112 (32.1)	<0.001	140 (53.4)	<0.001
Pleural metastasis, n (%)	191 (43.3)	33 (35.9)	158 (45.3)	0.105	67 (25.6)	<0.001
Type of brain and leptomeningeal metastasis, n (%)				–		–
Single	–	19 (20.7)	–		45 (17.2)	
Multiple	–	52 (56.5)	–		204 (78.2)	
Leptomeningeal	–	5 (5.4)	–		3 (1.1)	
Single + Leptomeningeal	–	1 (1.1)	–		3 (1.1)	
Multiple + Leptomenigenal	–	15 (16.3)	–		6 (2.3)	

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; AJCC, American Joint Committee on Cancer.

Table 2 Cumulative incidence (%) of CNS failure[1] in patients without brain metastases at baseline

Parameter	Univariate analysis (CI, %)			P
	1 year	2 years	3 years	
Overall (n=441)	10.1	21.5	30.0	
Sex				0.962
Male (n=242)	13.2	22.5	28.5	
Female (n=199)	6.5	18.5	32	
Age (years)				0.456
<65 (n=229)	12.6	24.1	31.0	
≥65 (n=212)	7.1	18.4	29.1	
Smoking status				0.895
Never (n=281)	7.8	21.5	30.1	
Former (n=119)	15.5	20.9	30.9	
Current (n=39)	11.6	25.0	29.1	
ECOG performance status				<0.001
0–1 (n=383)	7.7	19.2	26.3	
≥2 (n=28)	39.9	56.8	78.4	
EGFR mutation				0.022
Del19 (n=259)	9.2	19.9	29.4	
L858R (n=138)	9.0	20.4	27.3	
Other[2] (n=44)	18.8	36.5	42.3	
No. of metastatic organs				<0.001
0–2 (n=386)	6.6	15.4	24.0	
3–6 (n=55)	33.8	61.6	69.3	
Stage (AJCC 8th edition)				<0.001
3–4A (n=302)	6.9	14.1	19.8	
4B (n=139)	16.7	37.7	53.7	
Liver metastasis				0.002
Yes (n=37)	18.0	41.8	53.0	
No (n=404)	9.3	19.6	27.8	
Bone metastasis				<0.001
Yes (n=160)	18.7	36.5	45.3	
No (n=281)	5.2	13.4	21.8	
Pleural metastasis				0.036
Yes (n=191)	5.9	14.7	22.0	
No (n=290)	13.3	26.9	35.1	

[1], CNS failure was defined as CNS progression e.g., appearance of new brain or leptomeningeal lesions during afatinib treatment; [2], compound plus uncommon mutations. CI, cumulative incidence; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; AJCC, American Joint Committee on Cancer.

Table 3 Factors affecting CNS failure[1] using a multivariate Cox-regression model

Parameter	HR	95% CI	P
Sex			
Male	Ref.	–	–
Female	0.83	0.47–1.46	0.51
Age (years)			
<65	Ref.	–	–
≥65	1.22	0.78–1.91	0.394
Smoking status			
Never	Ref.	–	–
Former	0.93	0.49–1.77	0.826
Current	1.08	0.48–2.42	0.854
ECOG performance status			
0–1	Ref.	–	–
≥2	5.98	3.26–10.99	<0.001
EGFR mutation			
Del19	Ref.	–	–
L858R	1.13	0.69–1.86	0.63
Other	3.07	1.61–5.83	0.001
No. of metastatic organs			
0–2	Ref.	–	–
3–6	4.65	2.56–8.45	<0.001
Stage (AJCC 8th edition)			
3–4A	Ref.	–	–
4B	1.21	0.67–2.16	0.528
Liver metastasis			
Yes	1.28	0.63–2.62	0.502
No	Ref.	–	–
Bone metastasis			
Yes	1.27	0.72–2.22	0.414
No	Ref.	–	–
Pleural metastasis			
Yes	0.56	0.35–0.90	0.017
No	Ref.	–	–

[1], CNS failure was defined as CNS progression, e.g., appearance of new brain or leptomeningeal lesions during afatinib treatment. CNS, central nervous system; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; AJCC, American Joint Committee on Cancer.

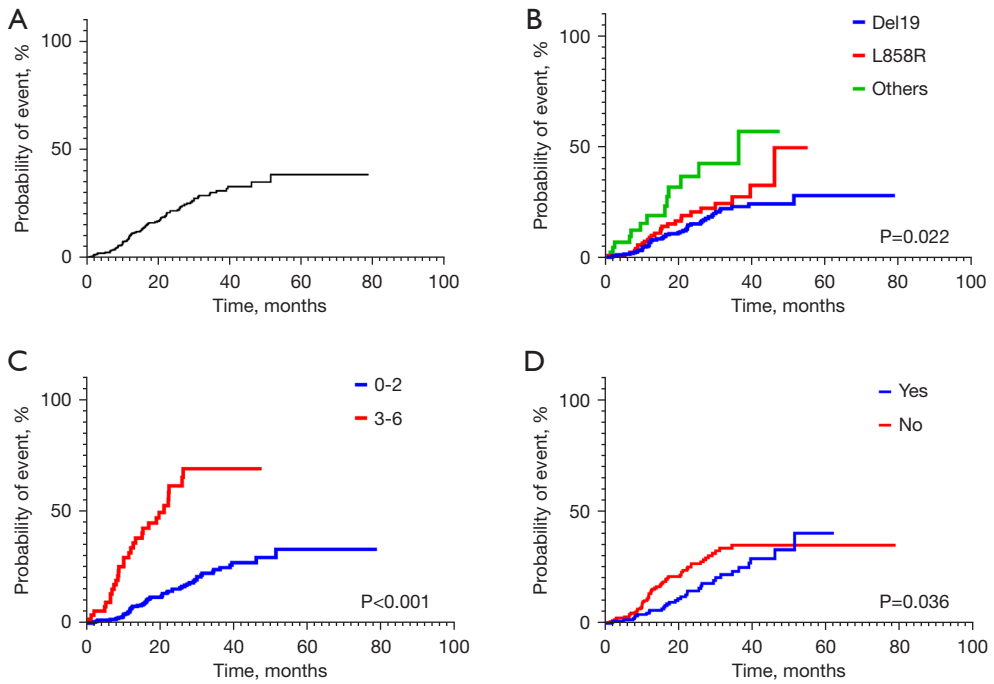

Figure 1 Cumulative incidence of CNS failure in patients without brain metastases at baseline. (A) Overall; (B) by *EGFR* mutation; (C) by number of metastatic organs involved (0–2 or 3–6); (D) presence (yes) or absence (no) of pleural metastasis. CNS failure was defined as the time from afatinib initiation until CNS progression, e.g., new brain or leptomeningeal lesions. CNS, central nervous system; EGFR, epidermal growth factor receptor.

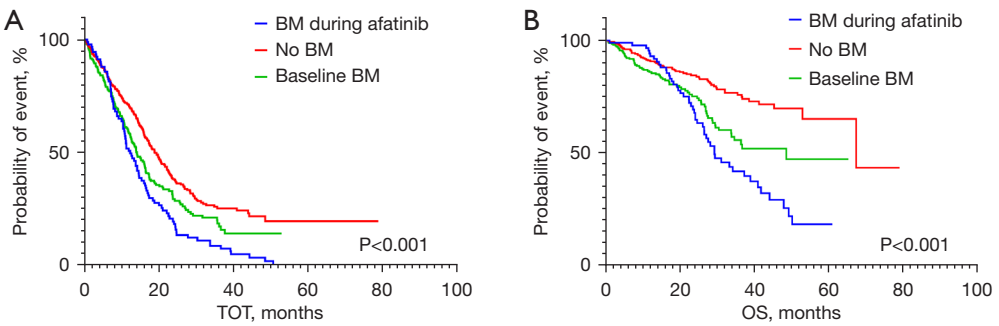

Figure 2 Kaplan-Meier survival curves of (A) TOT; and (B) OS by BM status. TOT, time on treatment; OS, overall survival; BM, brain metastasis.

failure during afatinib treatment. These results are similar to those from a real-world study of first-line afatinib in Asian patients with *EGFR* mutation-positive NSCLC (n=422) which reported that 17.7% of patients without baseline BMs subsequently developed BMs after starting afatinib treatment (31). In contrast to real-world studies, the risk of *de novo* CNS progression with afatinib estimated from analysis of the LUX-Lung 3 and LUX-Lung 6 clinical trials was much lower—6% (24).

Reported rates of CNS failure with other EGFR TKIs were also variable. A retrospective study of patients in the USA with advanced NSCLC treated with the first-generation EGFR TKIs gefitinib or erlotinib (n=100), reported a crude incidence rate for CNS progression of 28%. Twenty of 28 patients developed *de novo* CNS metastases (32). Continued follow-up of this cohort for a

median of 25 months found that a third developed CNS progression including 26 patients (26%) without baseline BMs, and the estimated 6-, 12-, and 24-month cumulative risk of CNS progression in patients without pre-existing BMs (n=77) was 1%, 3%, and 15%, respectively (33). Retrospective analysis of Korean patients with advanced NSCLC (n=232) reported a CNS failure rate of 16% for first-generation EGFR TKIs (gefitinib or erlotinib). Interestingly, isolated CNS failure was significantly more frequent in patients having clinical benefit from TKI treatment (n=127) than those who did not show clinical benefit (13% *vs.* 1%) (34). A retrospective study of Japanese patients with *EGFR*-mutated NSCLC treated with first-line gefitinib (n=144) or erlotinib (n=26) the incidence of CNS metastases was lower in the erlotinib group (11.5% *vs.* 29.9%). In patients with no baseline CNS metastases, CNS failure rates were 4.8% and 24.5%, respectively (35). *Post hoc* analysis of the Chinese ADJUVANT trial reported that CNS metastasis occurred in 27.4% (29/106) of patients receiving adjuvant gefitinib therapy in resected early-stage *EGFR*-mutation positive NSCLC (36). The multinational ARCHER 1050 trial, which compared the second-generation irreversible EGFR TKI dacomitinib with gefitinib in patients with advanced NSCLC and activating *EGFR* mutations, *de novo* BMs developed in 0.4% (1/227) and 4% (9/225) of patients, respectively (37,38). Similar CNS failure rates were found in Asian patients enrolled in the ARCHER 1050 trial: 0.6% and 4.5%, respectively (39). In contrast to the LUX-Lung 3 and LUX-Lung 6 trials, which included patients with clinically asymptomatic and controlled BMs (8,9), the ARCHER 1050 trial excluded patients with CNS metastases (39). In the multinational FLAURA trial, events of CNS progression in patients with *EGFR* mutation-positive advanced NSCLC treated with the third-generation, irreversible EGFR TKI, osimertinib or first-generation EGFR TKIs (gefitinib or erlotinib) were observed in 6% and 15%, respectively (40). Preclinical studies show osimertinib has greater penetration of the rodent blood-brain barrier than other *EGFR* TKIs (21,41), which may explain these results. However, there are no studies which directly compare the incidence of CNS failure in patients with metastatic NSCLC treated with osimertinib or afatinib.

This study demonstrated the clinically meaningful effectiveness of first-line afatinib which produced a median TOT of 16.0 months and median OS of 52.9 months. These effectiveness results are comparable to results from a recent meta-analysis of real-world studies of afatinib treatment for advanced *EGFR*-mutant NSCLC which calculated a median time to failure (TTF) for first-line afatinib (4 studies) of 15.7 months and, in seven studies of first- and further-line afatinib, median OS was 31.6 months although there was significant heterogeneity between studies (42). Data presented in this study also support those from the LUX-Lung clinical trial program, in particular the LUX-Lung 3 (8), 6 (9) and 7 (10,42) trials which demonstrated the efficacy of afatinib including in patients with asymptomatic BMs at baseline (12–16% of all patients). In the multinational LUX-Lung 3 trial which included both Asian and non-Asian patients, median PFS in afatinib-treated patients with *vs.* without BMs was 11.1 *vs.* 13.8 months; in the LUX-Lung 6 study of Asian patients was 8.2 *vs.* 11.1 months; and in the multinational LUX-Lung 7 study was 7.2 *vs.* 12.7 months (10,23). In a combined analysis of LUX-Lung 3 and 6 trials, afatinib significantly improved PFS compared with chemotherapy in patients with BMs (8.2 *vs.* 5.4 months; P=0.0297) (23). In the LUX-Lung 7 trial, there was a significant difference in PFS between afatinib and gefitinib, favoring afatinib, in pre-planned subgroups which included the presence versus absence of baseline BMs (10), although there was no significant difference in OS (43). Results from a recent prospective non-interventional study in Germany of patients with *EGFR*-mutant NSCLC (including approximately one third with baseline BMs) support clinical trial data for first-line afatinib in routine clinical practice: median PFS and median OS were 12.2 and 30.4 months, respectively (44).

Real-world studies of Asian patients with *EGFR* mutation-positive advanced NSCLC, including those with BMs, have also demonstrated the effectiveness of first-line afatinib. These include a retrospective review of electronic case reports from patients with advanced *EGFR* mutation-positive NSCLC (n=422) including 39.8% with BMs at diagnosis in South Korea. Median time to treatment discontinuation was significantly longer in patients without *vs.* with BMs (22.9 *vs.* 14.8 months, P=0.001) and OS was also prolonged in patients without BMs (not reached *vs.* 40.3 months, P=0.0009) (31). In a Taiwanese study, first-line afatinib (n=115) compared to gefitinib (n=116), had superior PFS (12.7 *vs.* 9.8 months; HR =0.59, P=0.001) and OS (39.1 *vs.* 22.0 months; HR =0.64, P=0.035) (45). Furthermore, in a Cox model adjusted for possible confounding factors, cumulative incidence of BM was lower for afatinib compared with gefitinib (HR =0.49, 95% CI: 0.34–0.71, P<0.001) although median PFS and median OS were comparable between the two TKIs in patients with baseline BMs (45). In a single center Korean

real-world study of patients with *EGFR*-mutant NSCLC (n=467) including 40% with BMs at baseline, median PFS for first-line afatinib was 19.1 months and was superior to that for first-line gefitinib (13.7 months) and erlotinib (14.0 months) (P=0.001) (46).

Our study showed that patients developing BMs had a poorer outcome than patients without CNS failure or with BMs at baseline, with significantly reduced TOT and OS. In most studies, among patients with *EGFR* mutation-positive NSCLC, patients with baseline BMs have a worse outcome compared to those without baseline BMs (18,47). However, in the present study, patients who developed *de novo* BMs showed a worse prognosis than patients with baseline BMs. Several theories have been proposed for the poor outcomes of CNS failures patients without baseline BMs. First, acquired resistance mutations against EGFR TKIs could induce CNS progression and poorer survival. The T790M mutation in the *EGFR* gene is the most common cause of resistance after first- or second-generation TKI therapy (48,49) and is localized within the ATP-binding pocket of EGFR. The primary cause of TKI resistance mediated by T790M mutant EGFR is its increased affinity for ATP (50). Resistance to EGFR TKIs can also result from mechanisms including transformation into small cell lung cancer (SCLC) and amplification of *MET* or *ERBB2* genes (51-53). Prognosis for newly developed CNS progression by these mechanisms may be worse than for patients with baseline BMs.

In NSCLC, brain is the third most common single metastatic site after bone and lung; and for two metastases, the most common sites are bone plus lung followed by bone plus brain (54). In this study, multivariate analysis of first-line afatinib in patients with *EGFR* mutation-positive NSCLC without BM revealed that CNS failure was associated with ECOG status, uncommon *EGFR* mutations, and pleural metastasis status. Retrospective studies of patients with *EGFR* mutation-positive advanced NSCLC have previously identified younger age (55,56), number of extracranial metastases (56), malignant pleural effusion (56), serum carcinoembryonic antigen (CEA) (55) and point mutations in *EGFR* exon 21 (55) as independent risk factors for BM. Recent data, from a large real-world cohort of NSCLC patients with common and uncommon EGFR mutations treated with first-line afatinib, showed that *EGFR* L858R patients had a significantly higher CNS progression; there was a tendency to higher CNS progression in patients with uncommon mutations excluding exon 20 insertion and de novo T790M with high allele frequency (57).

Our analysis showed that pleural metastases were present in 26% of cases with initial BMs and 43% of cases without initial BMs, which differs from the high incidence of metastases to other organs (liver, bone) in the presence of initial BMs. Moreover, the absence of pleural metastases was a risk factor for the development of BMs. There may be differences in the organs that metastasise depending on the characteristics of the patient's lung cancer, so patients with pleural metastases may have characteristics that make them less likely to develop BMs. Similarly, Li *et al.* (58), found that patients with BMs from NSCLC had more liver, lymph node, and adrenal metastases, but fewer pleural metastases, compared with patients without BMs. And in both univariate and multivariate analyses, the absence of pleural metastases was a risk factor for brain or leptomeningeal metastases (brain pleural metastases, OR: 0.495, 95% CI: 0.325–0.756; leptomeningeal metastases, OR (0.307, 95% CI: 0.172–0.547). In contrast, Ouyang *et al.* (56), found that in CNS failure in patients without BMs, pleural metastasis was a risk factor in univariate and multivariate analysis (OR: 5.283, 95% CI: 1.851–15.053). An alternative hypothesis is that afatinib is so effective against pleural metastases that it prevents deterioration that could lead to BMs. Further studies are needed to assess the relationship between pleural effusion and the risk for developing BMs, and the associated underlying mechanism.

Several risk factors for *EGFR* mutation-positive advanced NSCLC are in common with previously identified risk factors for BM in NSCLC. Factors include EGFR mutation-positive status (59), younger age (60), non-squamous cell carcinoma, especially adenocarcinoma (60-62), advanced stage disease (59), lesion diameter of the primary tumor (63), and elevated serum levels of NSE (60,62), CEA (60,63), CA125 (60) and calcium (63).

Limitations of this non-interventional, retrospective observational study are the potential variable quality and integrity of data, including length of follow-up, in patient electronic records which were reviewed. Importantly, because brain imaging data were not analyzed further in this study, there is a possibility that BMs were missed in patients classified as being without baseline BMs. This may have an impact in assessing the cumulative incidence of CNS failure in patients without baseline BMs. Additionally, although we collected data on the type of BMs, we did not investigate the type of local treatment. Although this is a limitation of our study, the combination of afatinib and local treatment for initial BMs is still controversial and is based on the judgement of medical staff. And if a patient without

BMs develops BMs after using afatinib, we assume that the best local treatment would have been chosen based on the patient's brain lesion status. Finally, the generalizability of our findings is limited by the fact that this real-world analysis only assessed data from patients across Korea.

Conclusions

First-line afatinib in the real-world setting in Korea showed clinically meaningful effectiveness in patients with *EGFR*-mutant NSCLC and BM. CNS failure during afatinib treatment was a poor prognostic factor for TOT and OS, correlating with younger age, poor ECOG PS, higher metastatic number, advanced disease stage, uncommon *EGFR* mutations, and baseline liver or bone metastases.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-832/coif). Sung Yong Lee has received honoraria from Boehringer Ingelheim for lectures. YSC is a stockholder of Big Bio Co., Ltd. The other authors have no conflicts of interest to declare.

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 and protocol were approved by the Institutional Review Board of the Kosin University Gospel Hospital (IRB, KUGH No. 2019-07-038). The other 15 participating hospitals were also informed and agreed with the study. This non-interventional, retrospective chart review study was carried out in compliance with the protocol and principles laid down in the Declaration of Helsinki (as revised in 2013), in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice and the relevant sponsor's Standard Operating Procedures. As this was a non-interventional, retrospective chart review study based on existing data in general practice, it did not require patient informed consent as per Korean regulations. Patient identification code numbers were used to ensure patient confidentiality.

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Supplementary

Table S1 Uncommon EGFR mutation status in patients

Parameter	No baseline brain metastases		Baseline brain metastases (n=262)	Total (n=703)
	New brain metastases (n=92)	No brain metastases (n=349)		
Major uncommon mutation				
G719X	4 (30.8)	12 (38.7)	5 (22.7)	21 (31.8)
L816Q	2 (15.4)	7 (22.6)	5 (22.7)	14 (21.2)
Compound				
G719X+S768I	3 (23.1)	4 (12.9)	4 (18.2)	11 (16.7)
T790M+sensitive mutations*	0 (0.0)	2 (6.5)	2 (9.1)	4 (6.1)
G719X+L861Q	0 (0.0)	2 (6.5)	1 (4.5)	3 (4.5)
19deletion+20insertion	1 (7.7)	1 (3.2)	0 (0.0)	2 (3.0)
T790M+G719X	1 (7.7)	0 (0.0)	0 (0.0)	1 (1.5)
19deletion+L861Q	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)
Exon 20 insertion	2 (15.4)	2 (6.5)	1 (4.5)	5 (7.6)
S768I	0 (0.0)	1 (3.2)	2 (9.1)	3 (4.5)
T790M	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)

*Sensitive mutations included EGFR 19 deletion and L858R mutation. EGFR, epidermal growth factor receptor

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Table S2 Time on treatment (TOT) according to brain metastasis status

Category	Total	Within-category P value[a]	New brain metastases (n=92)	No brain metastases (n=349)	Baseline brain metastases (n=262)	Brain metastasis status P value[b]
Overall	16.0 (14.8–17.2)	–	12.2 (9.9–14.6)	18.9 (16.8–21.0)	14.1 (11.9–16.3)	<0.001
Sex						
Male	15.0 (13.3–16.6)	0.235	11.2 (8.8–13.5)	17.4 (15.4–19.4)	13.8 (12.1–15.6)	0.016
Female	16.4 (14.0–18.9)		13.7 (9.3–18.2)	21.4 (18.7–24.1)	15.2 (12.8–17.6)	<0.001
Age (years)						
<65	16.1 (14.6–17.6)	0.308	11.0 (7.6-14.4)	19.3 (15.2-23.4)	15.0 (13.1-16.8)	<0.001
≥65	16.0 (13.9–18.1)		12.6 (10.5-14.7)	18.9 (15.6-22.2)	12.6 (8.6-16.6)	0.027
Smoking status						
Never	16.9 (15.1–18.7)	0.185	13.7 (9.9–17.6)	21.4 (18.7–24.2)	14.1 (11.4–16.7)	<0.001
Former	13.9 (11.0–16.7)		10.4 (7.5–13.2)	15.8 (12.0–19.6)	16.2 (10.6–21.9)	0.025
Current	14.4 (13.4–15.5)		13.7 (10.7–16.8)	23.6 (12.6–34.6)	5.7 (NA–11.7)	0.074
ECOG performance status						
0–1	16.4 (15.0–17.8)	0.001	13.3 (9.3–17.2)	18.9 (16.4–21.3)	15.2 (13.4–17.0)	0.001
≥2	10.8 (6.2–15.4)		8.2 (6.2–10.1)	17.9 (13.7–22.1)	10.4 (5.9–14.9)	0.225
EGFR mutation						
Del19	16.2 (14.8–17.6)	0.049	12.2 (9.1–15.4)	20.7 (16.5–25.0)	13.8 (11.1–16.6)	<0.001
L858R	16.3 (13.9–18.7)		16.2 (14.8–17.6)	13.7 (9.5–18.0)	18.8 (15.6–22.0)	0.335
Other	10.8 (6.2–15.4)		7.1 (5.2–18.8)	12.0 (5.2–18.8)	13.5 (2.1–24.9)	0.311
Number of metastatic organs						
0–2	17.0 (15.6–18.5)	<0.001	14.1 (11.5–16.8)	19.4 (16.9–21.8)	13.9 (11.4–16.4)	0.002
3–6	12.8 (11.0–14.5)		8.2 (4.0–12.3)	15.8 (9.7–21.9)	14.1 (11.5–16.7)	0.013
Stage (AJCC 8th edition)						
3–4A	17.5 (15.5–19.5)	0.008	12.6 (8.1–17.1)	19.3 (17.1–21.5)	16.4 (12.0–20.8)	0.034
4B	14.2 (12.6–15.7)		11.9 (9.3–14.4)	18.8 (13.0–24.5)	13.4 (11.8–14.9)	<0.001
Baseline liver metastasis						
Yes	10.9 (7.6–14.3)	<0.001	7.5 (6.0–8.9)	13.7 (8.1–19.3)	10.1 (6.1–14.1)	0.148
No	16.6 (15.1–18.1)		13.3 (10.5–16.1)	19.7 (17.1–22.2)	15.6 (13.5–17.8)	<0.001
Baseline bone metastasis						
Yes	14.4 (12.9–16.0)	0.024	10.0 (6.2–13.8)	17.3 (13.0–21.6)	14.2 (12.1–16.2)	0.001
No	17.0 (15.0–19.1)		14.1 (12.6–15.6)	19.4 (16.7–22.1)	13.7 (10.5–16.8)	0.011
Baseline pleural metastasis						
Yes	17.3 (15.5–19.1)	0.914	14.6 (8.4–20.7)	18.0 (15.5–20.5)	15.2 (10.7–19.7)	0.186
No	15.2 (13.8–16.5)		11.0 (8.7–13.3)	20.6 (16.5–24.7)	13.9 (11.7–16.0)	<0.001

Values shown are months (95% CI). [a], P calculated by comparing values within each category (Male vs Female; <65 vs ≥65 years etc.). [b], P calculated by the log-rank test for new brain metastasis, no brain metastasis and baseline brain metastasis groups. AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

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Table S3 Overall survival (OS) according to brain metastasis status

Category	Total	Within-category P value[a]	New brain metastases (n=92)	No brain metastases (n=349)	Baseline brain metastases (n=262)	Brain metastasis status P value[b]
Overall	52.9 (45.4–60.3)	–	29.1 (23.3–35.0)	67.3 (43.7–90.9)	48.5 (NA–NA)	<0.001
Sex						
Male	67.3 (36.8–97.8)	0.162	27.5 (24.8–30.1)	67.3 (46.9–87.7)	28.6 (NA–NA)	<0.001
Female	50.0 (NA–NA)		38.8 (22.5–55.1)	NR (NA–NA)	48.5 (NA–NA)	0.001
Age (years)						
<65	67.3 (35.8–98.8)	0.469	29.1 (24.1–34.2)	67.3 (30.9–103.7)	NR (NA–NA)	<0.001
≥65	50.0 (44.8–55.3)		34.0 (16.2–51.9)	NR (NA–NA)	48.5 (20.9–76.0)	0.02
Smoking status						
Never	52.9 (41.6–64.1)	0.367	37.2 (22.1–52.2)	67.3 (43.0–91.6)	36.6 (22.6–50.6)	<0.001
Former	47.8 (37.0–58.6)		27.5 (16.2–38.7)	NR (NA–NA)	NR (NA–NA)	0.002
Current	NR (NA–NA)		29.1 (23.7–34.5)	NR (NA–NA)	NR (NA–NA)	0.232
ECOG performance status						
0–1	67.3 (43.9–90.7)	0.016	NA (NA–NA)	NA (NA–NA)	NA (NA–NA)	<0.001
≥2	26.8 (15.9–37.6)		NA (NA–NA)	NA (NA–NA)	NA (NA–NA)	0.07
EGFR mutation						
Del19	67.3 (39.2–95.4)	<0.001	30.9 (24.2–37.7)	NR (NA–NA)	NR (NA–NA)	<0.001
L858R	41.7 (34.2–49.1)		27.5 (23.4–31.5)	52.9 (35.4–70.4)	29.4 (NA–NA)	0.021
Other	33.7 (22.2–45.3)		24.5 (10.8–38.2)	NR (NA–NA)	33.7 (22.2–45.3)	0.801
Number of metastatic organs						
0–2	67.3 (43.7–90.9)	<0.001	34.0 (23.1–44.9)	67.3 (43.7–90.9)	NR (NA–NA)	<0.001
3–6	29.3 (26.1–32.4)		26.4 (21.8–30.9)	NR (NA–NA)	29.3 (25.5–33.1)	0.302
Stage (AJCC 8th edition)						
3–4A	67.3 (43.7–90.9)	0.001	37.2 (25.3–49.0)	67.3 (43.6–91.0)	NR (NA–NA)	0.002
4B	36.6 (27.0–46.3)		26.4 (23.1–29.6)	NR (NA–NA)	33.7 (25.6–41.8)	0.002
Baseline liver metastasis						
Yes	28.7 (21.6–35.8)	<0.001	23.7 (22.8–24.5)	45.2 (25.8–64.6)	27.2 (22.6–31.7)	0.189
No	67.3 (42.8–91.8)		30.9 (24.8–37.1)	67.3 (NA–NA)	NR (NA–NA)	<0.001
Baseline bone metastasis						
Yes	33.1 (27.8–38.5)	<0.001	26.3 (22.5–30.2)	67.3 (NA–NA)	30.3 (25.3–35.3)	0.001
No	NR (NA–NA)		41.7 (34.2–49.1)	NR (NA–NA)	NR (NA–NA)	0.005
Baseline pleural metastasis						
Yes	52.9 (NA–NA)	0.244	38.8 (29.2–48.4)	NR (NA–NA)	48.5 (21.3–75.7)	0.01
No	67.3 (36.9–97.7)		26.3 (21.7–31.0)	67.3 (NA–NA)	NR (NA–NA)	<0.001

Values shown are months (95% CI). AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NA, not available; NR, not reached. [a], P calculated by comparing values within each category (Male vs Female; <65 *vs.* ≥65 years etc.). [b], P calculated by the log-rank test for new brain metastasis, no brain metastasis and baseline brain metastasis groups.

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