Clinical outcome analysis of different first- and second-generation EGFR-tyrosine kinase inhibitors in untreated patients with EGFR-mutated non-small cell lung cancer with baseline brain metastasis

CHEN-CHUAN HSU[1], LI-CHUNG CHIU[1,2], HOW-WEN KO[1,2], CHIAO-EN WU[2,3], SCOTT CHIH-HSI KUO[1,2], JIA-SHIUAN JU[1], ALLEN CHUNG-CHENG HUANG[1], CHIN-CHOU WANG[2,4], CHENG-TA YANG[1,5,6] and PING-CHIH HSU[1,2]

[1]Division of Thoracic Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan 33305, Taiwan, R.O.C.; [2]Department of Medicine, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan, R.O.C.; [3]Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan 33305, Taiwan, R.O.C.; [4]Department of Pulmonary and Critical Care Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 83301, Taiwan, R.O.C.; [5]Department of Internal Medicine, Taoyuan Chang Gung Memorial Hospital, Taoyuan 33378, Taiwan, R.O.C.; [6]Department of Respiratory Therapy, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan, R.O.C.

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Abstract. Currently, the clinical outcomes of patients with epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) with baseline brain metastasis receiving first- and second-generation EGFR-tyrosine kinase inhibitors (TKIs) are not clear. The present study aimed to assess the clinical outcomes of patients with EGFR-mutated NSCLC with baseline brain metastasis who received first-line first- and second-generation EGFR-TKIs. In the present study, a retrospective analysis of clinical charts was performed to investigate first- and second-generation EGFR-TKIs in patients with *EGFR*-mutated NSCLC with baseline brain metastasis. Data from 197 patients with *EGFR*-mutated NSCLC with baseline brain metastasis who received first-line gefitinib, erlotinib or afatinib between May 2013 and January 2020 were retrieved from the Cancer Center database of Chang Gung Memorial Hospital at Linkou for analysis. The systemic objective response rate and intracranial response rate to first-line EGFR-TKIs were 75.1 and 76.1%, respectively. The median progression-free survival (PFS) with first-line EGFR-TKIs, brain metastasis PFS (BMPFS) and overall survival (OS) of all the included patients were 13.07 [95% confidence interval (CI), 11.43-14.70], 24.63 (95% CI, 20.98-28.28) and 28.13 months (95% CI, 23.53-32.74), respectively. According to multivariate analysis, a greater number of brain metastases (>3) and the presence of leptomeningeal carcinomatosis (LMC) were independent predictors of a shorter PFS. Patients with a greater number of brain metastases or LMC also had markedly shorter BMPFS and OS than those with fewer brain metastases or no LMC. First- and second-generation EGFR-TKIs were effective for treating previously untreated patients with *EGFR*-mutated NSCLC with baseline brain metastasis. In conclusion, for patients whose unfavorable factors [a greater number of brain metastases (>3) and LMCs] are associated with worse clinical outcomes, upfront osimertinib therapy, alone or in combination with other therapeutic strategies and procedures, should be considered.

Correspondence to: Dr Ping-Chih Hsu, Division of Thoracic Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, 5 Fuxing 1st Road, Guishan, Taoyuan 33305, Taiwan, R.O.C.
E-mail: 8902049@gmail.com; 8902049@adm.cgmh.org.tw

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Introduction

Epidermal growth factor receptor (*EGFR*) gene mutations account for most cancer-related genomic alterations in cases of non-small cell lung cancer (NSCLC) in East Asia, as the incidence rate ranges from 45-55% (1,2). A single amino acid substitution of leucine to arginine at site 858 in exon 21 (L858R mutation) and an in-frame deletion within exon 19 (exon 19 deletion) account for ~90% of all *EGFR* mutations in NSCLC. Other *EGFR* mutations, including G719X in exon 18, S768I in exon 20 and L861Q in exon 21, have been detected and classified as major uncommon *EGFR* mutations (5-7% of all *EGFR* mutations) (3,4). *EGFR* mutations, including common (L858R and exon 19 deletion) and major uncommon (G719X, S768I and L861Q) mutations, alter the activity of the intracellular tyrosine kinase domain of EGFR and promote downstream pro-survival signaling pathways in NSCLC (3-7).

In the past 2 decades, EGFR-tyrosine kinase inhibitors (TKIs) have been developed and reported to be effective at suppressing the growth of human NSCLC cells with common and major uncommon *EGFR* mutations (3,4,6-8). First- and second-generation EGFR-TKIs, including gefitinib, erlotinib and afatinib, have shown promising anticancer efficacy in advanced *EGFR*-mutated NSCLC [60-80% objective response rate (ORR) and 9-13 months of progression-free survival (PFS)] in several previous prospective clinical trials and real-world clinical analyses (6-10). Therefore, first- and second-generation EGFR-TKIs are used as standard first-line treatments for patients with advanced NSCLC with *EGFR* mutations (3,4,6-10).

Brain metastasis is the main morbidity that frequently occurs in patients with NSCLC, and 20-40% of patients with NSCLC experience this complication throughout the course of their disease (11,12). A previous extensive clinical analysis reported that patients with NSCLC harboring *EGFR* mutations had increased incidence of brain metastasis compared with those harboring wild-type *EGFR* (13). Previous studies have reported that first- and second-generation EGFR-TKIs have good blood-brain barrier (BBB) permeability and can effectively control the brain metastasis of *EGFR*-mutated NSCLC (14,15). However, in previous large prospective clinical trials, only asymptomatic or stable symptomatic control patients with previously treated brain metastases were allowed to be recruited (6-10). Although the brain metastasis of *EGFR*-mutated NSCLC has been included in previous real-world retrospective studies for analysis, these previous studies reported that brain metastasis was an unfavorable prognostic factor or reported the effects of additional local therapies on brain metastasis (7,9,12,15). In clinical practice, certain patients with brain metastasis of *EGFR*-mutated NSCLC have neurological symptoms induced by brain metastasis and have to receive local therapies (radiation therapy or neurosurgery) and EGFR-TKIs concurrently (12-15). In addition, first- and second-generation EGFR-TKIs have been widely used for the treatment of patients with advanced *EGFR*-mutated NSCLC in clinical practice over the past two decades (6-10).

Therefore, the present study aimed to assess the clinical outcomes of patients with *EGFR*-mutated NSCLC with baseline brain metastasis who received first-line first- and second-generation EGFR-TKIs. In addition, the efficacy of different EGFR-TKIs were compared and predictive clinical factors associated with survival outcomes were identified.

Patients and methods

Patients, EGFR mutation detection, treatment and follow-up. Data was retrieved from the Cancer Center of Chang Gung Memorial Hospital at Linkou (Taoyuan, Taiwan) database. Between May 2013 and January 2020, 1,034 patients with histologically diagnosed stage IV NSCLC harboring *EGFR* mutations who received first-line first- and second-generation EGFR-TKIs were retrospectively screened. Ultimately, 197 patients were included in the analysis, and the inclusion criteria for further analysis were as follows: i) Brain metastasis detected at the time of the initial diagnosis of NSCLC; ii) common *EGFR* mutations (exon 19 deletion and L858R); iii) first- and second-generation EGFR-TKIs alone used as the first-line therapy for NSCLC; iv) contrast-enhanced brain magnetic resonance imaging (MRI) performed at the time of the initial diagnosis of NSCLC that could be used as a baseline image to assess the size and number of brain metastases; and v) systemic treatment-naïve status (no previous systemic treatment such as targeted therapy, chemotherapy or immunotherapy). Patients meeting the following criteria were excluded from the analysis in the present study: i) No brain metastasis at the initial diagnosis of NSCLC; ii) uncommon *EGFR* mutations (such as G719X, L861Q and S768I); iii) treatment with EGFR-TKIs combined with anti-angiogenic agents (such as bevacizumab or ramucirumab); iv) no contrast-enhanced brain MRI data available as baseline images; and v) previous treatment with any systemic therapies, including targeted therapy, chemotherapy or immunotherapy. The process of selecting study subjects for the final analysis is summarized in Figure 1.

EGFR mutations of patients [189 patients (95.9%)] in the present study were mainly detected using an amplified refractory mutation system-Scorpion assay (ARMS/S). A number of patients [8 patients (4.1%)] had primary *EGFR* mutations detected by direct sequencing, the method of which has been described previously (16) (Figs. S1 and S2). The procedures of ARMS/S and direct sequencing were performed by the Central Molecular Lab of Department of Pathology (Chang Gung Memorial Hospital), a College of American Pathologists-accredited laboratory. The DNA used for EGFR testing were extracted from formalin-fixed paraffin-embedded tumor tissues or cytology blocks, and DNA extraction were performed using the DEXPAT kit (Takara Bio, Inc.) following the manufacturer's instructions. The ABI BigDye Terminator kit version 3.1 (cat. no. 4337458; Applied Biosystems; Thermo Fisher Scientific, Inc.) was used for EGFR detection via direct sequencing, and the EGFR Plus RGQ PCR Kit (cat. no. 874601; Qiagen, Inc.) was used for EGFR detection in ARSMS/S.

The primer sequences used were as follows: Exon 18 forward (F), 5'-TCCAAATGAGCTGGCAAGTG-3' and reverse (R), 5'-TCCCAAACACTCAGTGAAACAAA-3'; exon 19 F, 5'-TCACAATTGCCAGTTAACGTCT-3' and R, 5'-CAGCAAAGCAGAAACTCACATC-3'; exon 20 F, 5'-ACTTCACAGCCCTGCGTAAAC-3' and R, 5'-ATGGGACAGGCACTGATTTGT-3'; and exon 21 F, 5'-ATGAACTACTTGGAGGACCGTC-3' and R, 5'-TGCCTCCTTCTGCATGGTATTC-3'.

All patients in the present study underwent brain MRI to assess the baseline status of brain metastasis, including the number of metastases, the largest diameter of the metastatic tumor and the presence or absence of leptomeningeal carcinomatosis (LMC). All study patients underwent contrast medium-enhanced computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) to determine the baseline disease status at diagnosis. Furthermore, they underwent whole-body CT every 3-4 months to evaluate the systemic treatment response to EGFR-TKIs. Brain MRI was performed on follow-up 3-6 months after treatment in most study patients [189 patients (95.9%)] to assess the intracranial treatment response. A small number of study patients [8 patients (4.1%)] did not receive follow-up brain MRI due to rapid disease progression and death. Other additional imaging tests, such as sonograms or FDG-PET, were ordered on the basis of the

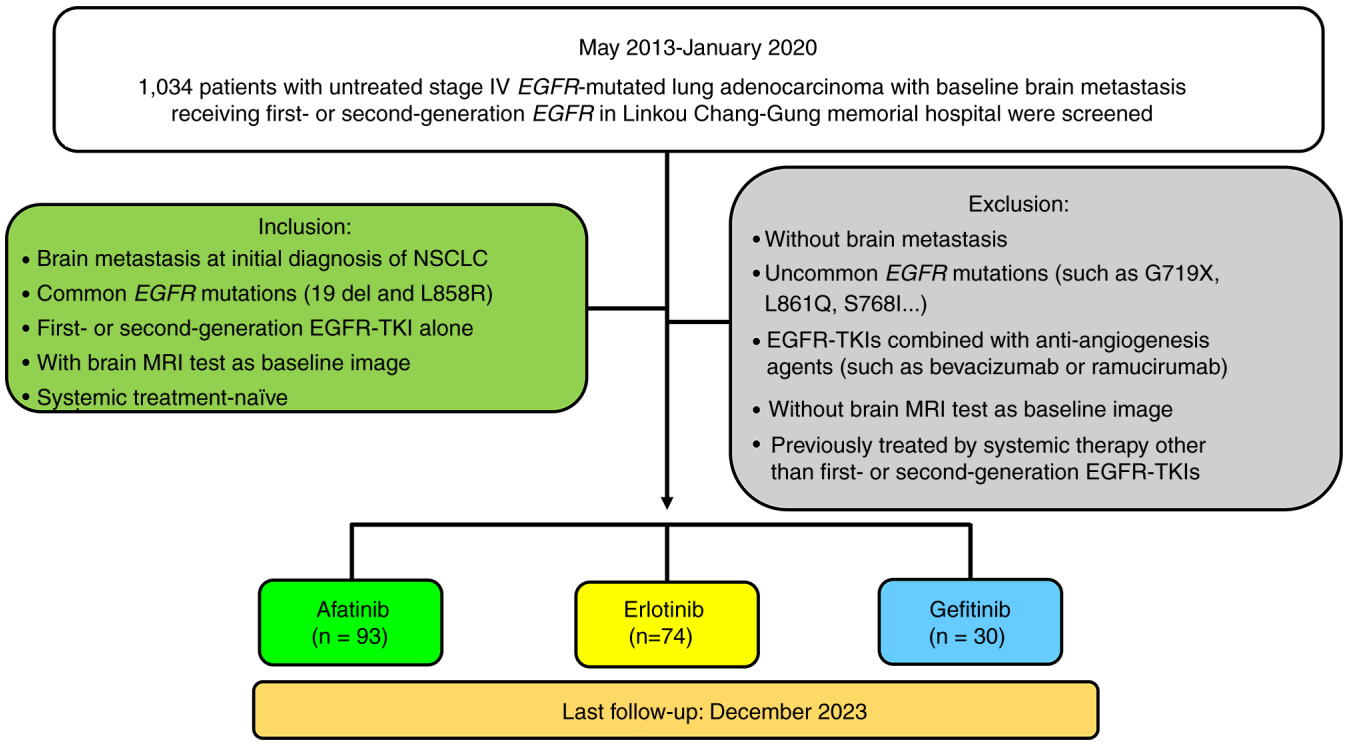

Figure 1. Inclusion and exclusion criteria for identifying study patients for analysis. *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

needs of clinical physicians to facilitate the evaluation of disease status.

All the treatment responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 3.0 and the responses were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). PFS was defined as the period between the date of first-line EGFR-TKI administration and the first image showing PD. The duration of brain metastasis-free survival was defined as the time from the first date of first-line EGFR-TKI treatment to the first date of progressive brain metastasis revealed by images or the date of mortality. Overall survival (OS) was measured from the first date of first-line EGFR-TKI administration to the date of mortality. If patients survived to the last follow-up time point (December 2023), PFS, brain metastasis-free survival and OS were censored at the last date of the clinical visit.

Brain metastasis-related symptoms and first-line EGFR-TKI treatment-related adverse events (AEs) were retrieved from electronic chart records and assessed according to the National Cancer Institute Common Terminology Criteria version 3.0 (17).

Statistical analysis. The baseline demographic characteristics and treatment modalities of the patients in the present study are presented as quantitative variables. Cox regression was used to analyze the predictive clinical variables associated with PFS in patients receiving first-line EGFR-TKI therapy. Both univariate and multivariate analyses were performed according to different clinical variables. For PFS, brain metastasis-free survival and OS data were analyzed using Kaplan-Meier survival curves. Kaplan-Meier survival curves with log-rank tests were also used to compare PFS, brain metastasis-free survival and OS among patients stratified according to different clinical variables. $P<0.05$ was considered to indicate a statistically significant difference. The statistical analysis in the present study was performed using SPSS Statistics version 22.0 (IBM Corp.). PFS, brain metastasis-free survival and OS curves were plotted using GraphPad Prism (version 5.0; Dotmatics).

Results

Baseline clinical characteristics and treatment information of all study patients. Among all the patients in the present study, 196 (99.5%) had histologically diagnosed adenocarcinoma and only one (0.5%) had adenosquamous cell carcinoma. Among the *EGFR* mutations, 118 (59.9%) were exon 19 deletion mutations and 79 (40.1%) were L858R mutations. Among the EGFR-TKIs used in first-line therapy, 30 patients (15.2%) were administered gefitinib, 74 patients (37.6%) were administered erlotinib and 93 (47.2%) patients were administered afatinib. A total of 17 patients (8.6%) had LMC at initial diagnosis. Regarding the early administration of local therapies for brain metastasis (neurosurgery and radiation therapy within 30 days before or after initiating first-line EGFR-TKIs), 47 patients (23.9%) had received neurosurgery and 187 (94.9%) had received radiation therapy to brain metastases. Radiation therapies and neurosurgery 30 days after starting first-line EGFR-TKIs were defined as salvage local therapies. In the present study, 27 patients (13.7%) received salvage radiation therapies to the brain and 14 (7.1%) received salvage neurosurgery. Among the 27 patients (13.7%) receiving salvage radiation therapies, 22 (11.2%) had received early radiation therapies to

the brain and among the 14 patients (7.1%) receiving salvage neurosurgery, 11 (5.6%) had received early radiation therapies to the brain.

The main symptoms related to brain metastasis were recorded in the present study, and the most frequent symptom was dizziness or vertigo (16.2%), followed by headache (12.2%), hemiplegia (8.1%), seizure (6.1%), conscious disturbance (3.6%), gait disturbance (3.0%) and visual disturbance (2.5%).

At the last follow-up in the present study (December 2023), 21 patients were still receiving first-line EGFR-TKI treatments and 176 patients experienced PD after first-line EGFR-TKI treatments. Among the 176 patients who experienced PD after first-line therapy, 103 (52.3%) had undergone tissue re-biopsies or circulating tumor DNA for secondary T790M mutation tests. A total of two patients (1%) underwent tissue re-biopsies, and small cell lung cancer (SCLC) transformation was found using histology; neither patient underwent *EGFR* T790M mutation tests. Among the 103 patients who underwent T790M tests, a total of 66 patients had positive results of *EGFR*-T790M mutations (64%). Among the 66 patients (33.5%) with positive T790M mutations, 60 (30.5%) received osimertinib as second-line therapy, 4 patients (2%) received aumolertinib (HS-10296) in clinical trials and the remaining 2 (1%) received platinum-based chemotherapy. Among the patients with negative or unknown T790M mutations, 48 (24.4%) received platinum-based doublet chemotherapy, 9 (4.6%) received single agent chemotherapy and 2 (1%) received erlotinib as second-line systemic therapy. Second-line anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) were administered to 3 patients (1.5%), with 2 (1%) receiving ICIs combined with chemotherapy and 1 (0.5%) receiving ICIs alone. A total of 50 patients (25.4%) did not receive any second-line anticancer agents after first-line EGFR-TKI PD and received supportive care.

The baseline clinical characteristics and treatment information of all the study patients are presented in Table I, and the subsequent treatment modalities after first-line PD treatment are summarized in Table II.

Efficacy of first-line EGFR therapies in systemic responses and brain metastasis. Among all 197 study patients who received first-line afatinib treatment, 1 (0.5%) achieved CR, 147 (74.6%) achieved PR, 26 (13.2%) achieved SD and 23 (11.7%) experienced PD. The systemic ORR and disease control rate (DCR) were 75.1 and 88.3%, respectively (Table III). In terms of the intracranial treatment response to first-line EGFR-TKI therapies, 26 patients (13.2%) achieved CR, 124 (62.9%) achieved PR, 33 (16.8%) achieved SD, 11 (5.6%) achieved PD and 3 were not evaluated. The intracranial ORR and DCR were 76.1 and 92.9%, respectively (Table III).

For the study patients overall, the median PFS of first-line EGFR-TKI treatments was 13.07 months [95% confidence interval (CI), 11.43-14.70; Fig. 2A], the median brain metastasis PFS (BMPFS) was 24.63 months (95% CI, 20.98-28.28; Fig. 2B) and the median OS was 28.13 months (95% CI, 23.53-32.74; Fig. 2C). The median PFS, BMPFS and OS among patients receiving different first-line EGFR-TKIs (gefitinib, erlotinib and afatinib) were analyzed. The median PFS times were 11.13 months (95% CI, 7.51-14.76), 11.53 months (95% CI, 10.06-13.01) and 14.63 months (95% CI, 13.19-16.07) for patients receiving first-line gefitinib, erlotinib and afatinib, respectively (log-rank test, P=0.007; Fig. 2D). The median BMPFS rates were 21.77 months (95% CI, 0.03-44.18), 24.40 months (95% CI, 20.76-28.38) and 25.83 months (95% CI, 20.41-31.26) for patients receiving first-line gefitinib, erlotinib and afatinib, respectively (log-rank test, P=0.730; Fig. 2E). The median OS rates were 28.80 months (95% CI, 9.03-48.57), 26.23 months (95% CI, 21.76-30.71) and 29.10 months (95% CI, 22.14-36.06) for patients receiving first-line gefitinib, erlotinib and afatinib, respectively (log-rank test, P=0.535; Fig. 2F).

The results indicate that first- and second-generation EGFR-TKIs were effective as first-line therapies in patients with *EGFR*-mutated NSCLC with baseline brain metastasis and that treatment with afatinib yielded significantly longer PFS compared with gefitinib and erlotinib.

Cox regression analysis of the clinical predictive factors associated with PFS after first-line EGFR-TKI treatment. The median PFS of patients receiving first-line EGFR-TKI treatment according to different clinical variables was analyzed using Cox regression, and the results are presented in Table IV. According to the univariate analysis, the clinical factors of the absence of baseline bone metastasis, fewer brain metastases (≤3), first-line afatinib use, early neurosurgery, early radiation therapy to the brain and the absence of baseline LMC were significantly associated with longer PFS. No significant difference in PFS was recorded among patients with and without salvage local therapies (salvage radiation therapies and neurosurgery). Using multivariate analysis, fewer brain metastases (≤3) and the absence of a baseline LMC were revealed to be independent predictors of longer PFS. In the present analysis, increased metastatic number (>3) and the presence of LMC were demonstrated to be independent unfavorable clinical factors associated with PFS in patients with *EGFR*-mutated NSCLC with baseline brain metastasis who received first- and second-generation EGFR-TKIs.

Comparisons of PFS, BMPFS and OS based on the number of brain metastases and LMC status. Patients were categorized according to the number of brain metastatic tumors (≤3 and >3) and those with or without baseline data to compare PFS, BMPFS and OS. Patients with fewer baseline brain metastatic tumors (≤3) had significantly longer PFS [15.67 vs. 10.97 months; hazard ratio (HR)=0.465; CI, 0.339-0.637; P<0.001; Fig. 3A], BMPFS (37.73 vs. 18.90 months; HR=0.325; CI, 0.235-0.451; P<0.001; Fig. 3B) and OS (45.50 vs. 21.70 months; HR=0.309; CI, 0.222-0.431; P<0.001; Fig. 3C) compared with those with more brain metastatic tumors (>3). After first-line EGFR-TKI treatment, patients without LMC had significantly longer PFS (13.43 vs. 8.20 months; HR=0.149; CI, 0.066-0.339, P<0.001; Fig. 3D), BMPFS survival (26.63 vs. 11.67 months; HR=0.047; CI, 0.018-0.124; P<0.001; Fig. 3E) and OS (31.80 vs. 11.30 months; HR=0.046; CI, 0.017-0.122, P<0.001; Fig. 3F) compared with those with LMC. The results of the present study demonstrate that patients with an increased number of metastases (>3) or LMC have significantly worse clinical outcomes compared with those with fewer metastases (≤3) or without LMC in terms

Table I. Baseline characteristics and treatment information for all patients in the present study.

Characteristic	Patients (n=197)
Sex	
Male	71 (36)
Female	126 (64)
Age, years	65.3±11.2
ECOG PS	
0-1	156 (79.2)
≥2	41 (20.8)
Smoking status	
Non-smoker	149 (75.6)
Former/current smoker	48 (24.4)
Histology	
Adenocarcinoma	196 (99.5)
Adenosquamous	1 (0.5)
EGFR mutations	
Exon 19 deletion	118 (59.9)
L858R	79 (40.1)
Concurrent metastatic sites other than brain metastasis	
Liver	36 (18.3)
Bone	113 (57.1)
Number of brain metastases	
≤3	92 (46.7)
>3	105 (53.3)
Largest diameter of brain metastatic tumor, cm	
<3	160 (81.2)
≥3	37 (18.8)
EGFR-TKI	
Gefitinib	30 (15.2)
Erlotinib	74 (37.6)
Afatinib	93 (47.2)
Early neurosurgery (within 30 days of initiating first-line EGFR-TKIs)	
Yes	47 (23.9)
No	150 (76.1)
Early radiation therapy to brain metastasis (within 30 days of initiating first-line EGFR-TKIs)	
Yes	187 (94.9)
No	10 (5.1)
Salvage neurosurgery (30 days after initiating first-line EGFR-TKIs)	14 (7.1)
Salvage radiation therapy to brain metastasis (30 days after initiating first-line EGFR-TKIs)	27 (13.7)
Leptomeningeal carcinomatosis	17 (8.6)
Neurological symptoms related to brain metastasis	
Dizziness or vertigo	32 (16.2)
Headache	24 (12.2)
Hemiplegia	16 (8.1)
Seizure	12 (6.1)
Conscious disturbance	7 (3.6)
Gait disturbance	6 (3.0)
Visual disturbance	5 (2.5)
No neurological symptoms	95 (48.2)

Data are presented as n (%) or mean ± standard deviation. ECOG PS, eastern cooperative oncology group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Table II. First subsequent treatments after first-line epidermal growth factor receptor-tyrosine kinase inhibitors in all patients in the present study.

A, Therapies and tests

Variable	Value
First-line EGFR-TKI therapy administered	21 (10.7)
Progressive disease after first-line EGFR-TKI therapy	176 (89.3)
EGFR T790M mutation tests (by tissue sample re-biopsy or ctDNA analysis)	
Yes	103 (52.3)
No	73 (37.1)
Small cell transformation	2 (1)
EGFR T790M mutation	
Positive	66 (33.5)
Negative	47 (23.9)
EGFR T790M mutation rate	64

B, Treatments after first-line EGFR-TKIs

Variable	Value
T790M mutation-positive	
Third-generation EGFR-TKIs	64 (32.5)
Osimertinib	60 (30.5)
Aumolertinib (HS-10296)	4 (2)
Platinum-base doublet chemotherapy	2 (1)
T790M mutation-negative and unknown	
Erlotinib	2 (1.0)
Platinum-base doublet chemotherapy	48 (24.4)
Single agent chemotherapy	9 (4.6)
Anti-PD-1/PD-L1 immune checkpoint inhibitors	3 (1.5)
Anti-angiogenesis agent	
Bevacizumab	5 (2.5)
Supportive care	50 (25.4)

Data are presented as n (%) or %. *EGFR*, epidermal growth factor receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PD, progressive disease; TKI, tyrosine kinase inhibitor; ctDNA, circulating tumor DNA.

Table III. Systemic and brain metastasis treatment responses to first-line epidermal growth factor receptor-tyrosine kinase inhibitors in all patients in the present study.

Variable	Patients (n=197)
Systemic treatment response	
Complete response	1 (0.5)
Partial response	147 (74.6)
Stable disease	26 (13.2)
Progressive disease	23 (11.7)
Objective response rate	75.1
Disease control rate	88.3
Intracranial treatment response	
Complete response	26 (13.2)
Partial response	124 (62.9)
Stable disease	33 (16.8)
Progressive disease	11 (5.6)
Not evaluated	3 (1.5)
Objective response rate	76.1
Disease control rate	92.9

Data are presented as n (%) or %.

of PFS, BMPFS and OS. A summary of the aforementioned results is presented in Fig. 4.

First-line first- and second-generation EGFR-TKI-related AEs. The AEs associated with first-line EGFR-TKIs are summarized in Table V. Among the 197 patients in the present study, skin toxicities such as rash and acne were the most common AEs (87.8%), followed by paronychia (61.9%), diarrhea (57.4%), stomatitis (45.2%), anorexia (34.0%) and nausea and vomiting (16.2%). Grade 3 AEs included skin toxicity (8.6%), diarrhea (5.1%), paronychia (1.5%) and stomatitis (1.1%). All grade 3 AEs in the present study were controlled by reducing the dose of EGFR-TKIs or temporally interrupting EGFR-TKI therapies and administering medicines for symptomatic relief (such as topical agents for skin toxicity and anti-diarrheal agents for diarrhea). No permanent discontinuation of EGFR-TKI due to severe AEs occurred in the present study. No cases of EGFR-TKI treatment-related mortality were recorded in the present study.

Overall, the safety of the first- and second-generation EGFR-TKIs in patients with *EGFR*-mutated NSCLC with brain metastasis is acceptable, and the AEs are manageable.

Discussion

The results of the present study demonstrate that first- and second-generation EGFR-TKIs are effective and safe first-line treatments for patients with *EGFR*-mutated NSCLC with baseline brain metastasis. The PFS of patients treated with the second-generation EGFR-TKI afatinib was significantly longer compared with patients treated with the first-generation EGFR-TKIs gefitinib and erlotinib, and afatinib was equally effective at controlling brain metastasis, as indicated by brain metastasis-free survival. A greater number of brain metastatic tumors (>3) and the presence of LMCs were revealed to be independent factors associated with shorter PFS after first-line EGFR-TKI treatment. In addition, at baseline, a greater number of brain metastatic tumors (>3) or the presence of LMC negatively affected brain metastasis-free survival and OS. The frequent AEs including skin toxicities, paronychia, diarrhea, stomatitis and gastrointestinal upset associated with first- and second-generation EGFR-TKIs in the present study are in line with previous studies, and the AEs in the present study were

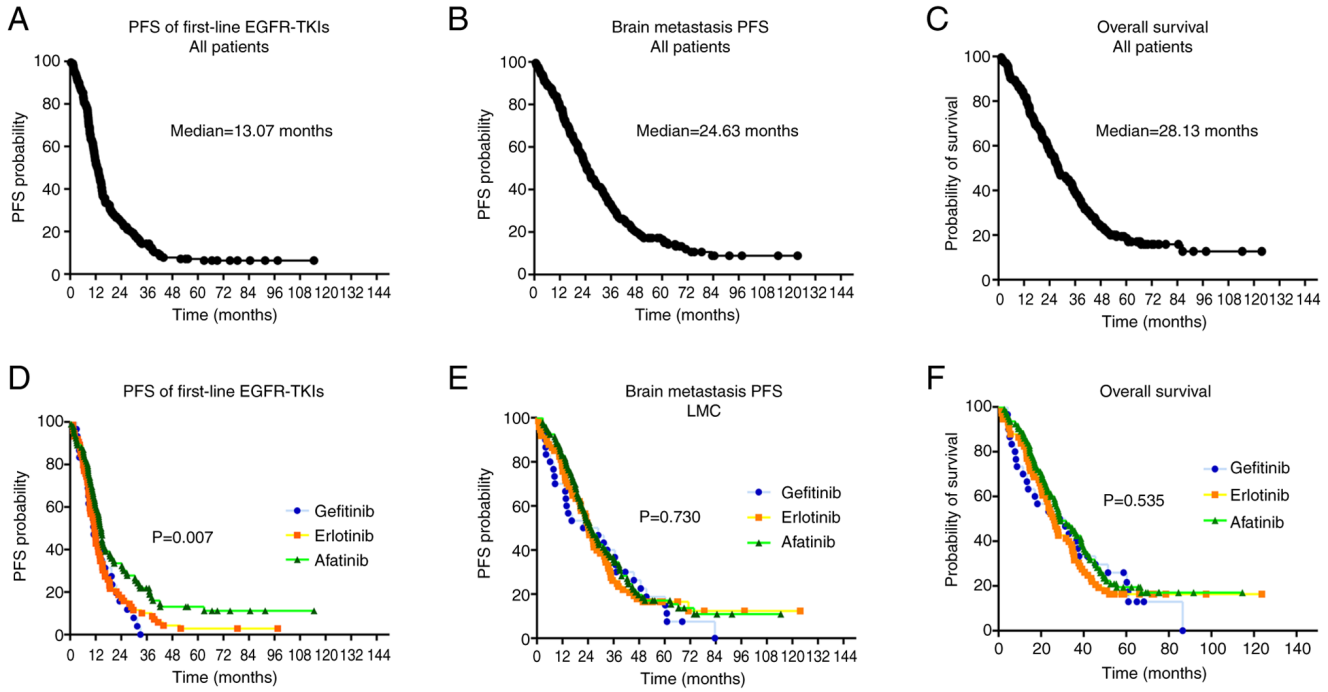

Figure 2. Analysis of PFS of first-line EGFR-TKIs, brain metastasis PFS and OS using Kaplan-Meier survival curves. Median (A) PFS, (B) brain metastasis PFS and (C) OS in all study patients. Analysis of (D) PFS, (E) brain metastasis PFS and (F) OS using Kaplan-Meier survival curves and the log-rank test in all study patients treated with different first-line first- and second-generation EGFR-TKIs. *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OS, overall survival; CI, confidence interval.

manageable (6-10). No AE-related permanent discontinuation or treatment-related mortality occurred in the present study.

Previous clinical studies have reported that first- and second-generation EGFR-TKIs, including gefitinib, erlotinib and afatinib, have improved effects on *EGFR*-mutated NSCLC brain metastases than conventional chemotherapy (18). In most previous clinical trials assessing EGFR-TKIs in patients with advanced *EGFR*-mutated NSCLC, patients with baseline brain metastasis were required to be asymptomatic or treated and stable before they entered the clinical trial (18). In real-world clinical practice, certain patients with *EGFR*-mutated NSCLC with baseline brain metastasis have neurological symptoms and have to receive additional radiation therapy or neurosurgery before or during EGFR-TKI treatment (12,18). An analysis of two previous retrospective studies suggested that brain metastasis resection surgery provided a survival benefit to patients with *EGFR*-mutated NSCLC receiving EGFR-TKI treatments (12,19). Our previous study revealed that neurosurgery had a median of 2 years of BMPFS for patients with brain metastasis with NSCLC who were candidates for surgery (12). Radiation therapies such as whole-brain radiotherapy and stereotactic body radiation therapy are important therapeutic modalities that are frequently administered to patients with NSCLC with brain metastasis. Previous studies have reported that brain radiation therapy, in addition to neurosurgery and targeted therapies, reduces the recurrence rate of brain metastasis and may improve OS in patients with brain metastatic NSCLC (19-22). Given local therapies (radiation therapies and neurosurgery) in addition to EGFR-TKIs benefit brain metastasis control (19-22), the majority of patients (94.9%) in the present study had received early brain radiation therapies (within 30 days of initiating first-line EGFR-TKI treatments). Certain patients (23.9%) had received early neurosurgery (within 30 days of initiating first-line EGFR-TKI treatments). The median BMPFS of 24.63 months was also comparable to the results reported in previous clinical studies (12,19-22).

Osimertinib is a third-generation EGFR-TKI that has been reported to have improved BBB permeability than first- and second-generation EGFR-TKIs in a previous preclinical study (23). In a pivotal clinical trial (FLAURA), osimertinib was reported to be associated with significantly longer PFS compared with gefitinib or erlotinib in untreated patients with *EGFR*-mutated NSCLC with central nervous system (CNS) metastasis (15.2 vs. 9.6 months) (24). The results of the FLAURA trial indicate that osimertinib may have improved efficacy against CNS metastasis compared with first-generation EGFR-TKIs (24). According to the protocol of the FLAURA trial, patients with CNS metastasis who were neurologically stable were eligible. In addition, any local treatment for brain metastasis or systemic steroid therapy was required to be completed >2 weeks before the initiation of trial treatment. Therefore, patients eligible for the FLAURA trial were relatively more neurologically stable than those in real-world practice (24). Moreover, a previous retrospective study by Huang *et al* (25) reported that osimertinib was not significantly superior to afatinib in terms of PFS from first-line therapy in patients with metastatic *EGFR*-mutated NSCLC. In the same study, patients with baseline brain metastasis treated with osimertinib had markedly longer PFS than patients treated with afatinib (25). The results of the study by Huang *et al* (25) suggest that osimertinib could be superior to afatinib in untreated patients with *EGFR*-mutated NSCLC with baseline brain metastasis. Given the concern about the cost-effectiveness of first- to third-generation EGFR-TKIs,

Table IV. Cox regression analysis of clinical factors associated with progression-free survival in patients receiving first-line epidermal growth factor receptor-tyrosine kinase inhibitors.

			Univariate analysis		Multivariate analysis	
Variable	n	Median PFS, months	HR (95% CI)	P-value	HR (95% CI)	P-value
Age			0.952 (0.694-1.307)	0.762	-	-
≤60 years	62	12.23				
>60 years	135	13.27				
Sex			1.056 (0.775-1.440)	0.729	-	-
Male	71	11.37				
Female	126	13.43				
ECOG PS			1.215 (0.848-1.740)	0.290	-	-
0-1	156	13.07				
≥2	41	13.27				
Smoking status			0.987 (0.695-1.401)	0.940	-	-
Non-smoker	149	13.43				
Former/current smoker	48	11.83				
EGFR mutations			0.792 (0.584-1.075)	0.135	-	-
L858R	79	11.63				
Exon 19 deletion	118	14.63				
Liver metastases			1.356 (0.931-1.976)	0.111	-	-
Yes	36	11.53				
No	161	13.40				
Bone metastases			1.504 (1.110-2.038)	0.008	-	-
Yes	113	11.63				
No	84	14.97				
Number of brain metastases			2.099 (1.537-2.865)	<0.001	1.782 (1.537-2.488)	0.001
≤3	92	15.67				
>3	105	10.97				
Largest diameter of brain metastatic tumor			0.938 (0.644-1.365)	0.738	-	-
<3 cm	160	12.13				
≥3 cm	37	14.97				
EGFR-TKIs			0.754 (0.615-0.923)	0.006	-	-
Gefitinib	30	11.13				
Erlotinib	74	11.53				
Afatinib	93	14.63				
Early neurosurgery			0.647 (0.452-0.926)	0.016	-	-
No	150	12.07				
Yes	47	16.50				
Early radiation therapy			0.527 (0.277-0.999)	0.050	-	-
No	10	8.63				
Yes	187	13.27				
Salvage neurosurgery			1.003 (0.570-1.767)	0.991	-	-
No	183	12.57				
Yes	14	14.63				
Salvage radiation therapy			0.972 (0.636-1.485)	0.894	-	-
No	170	13.07				
Yes	27	13.07				
Leptomeningeal carcinomatosis			3.105 (1.857-5.193)	<0.001	2.451 (1.433-4.184)	0.001
No	180	8.20				
Yes	17	13.43				

CI, confidence interval; ECOG PS, eastern cooperative oncology group performance status; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

Table V. Treatment-related adverse events associated with first- and second-generation epidermal growth factor receptor-tyrosine kinase inhibitors.

Adverse event	All (n=197)	Grade		
		1-2	3	4
Skin rash/acne	173 (87.8)	156 (79.2)	17 (8.6)	0 (0.0)
Paronychia	122 (61.9)	119 (60.4)	3 (1.5)	0 (0.0)
Diarrhea	113 (57.4)	103 (52.3)	10 (5.1)	0 (0.0)
Stomatitis	89 (45.2)	87 (44.2)	2 (1.1)	0 (0.0)
Anorexia (decreased appetite)	67 (34.0)	67 (34.0)	0 (0.0)	0 (0.0)
Nausea or vomiting	32 (16.2)	32 (16.2)	0 (0.0)	0 (0.0)

Data are presented as n (%).

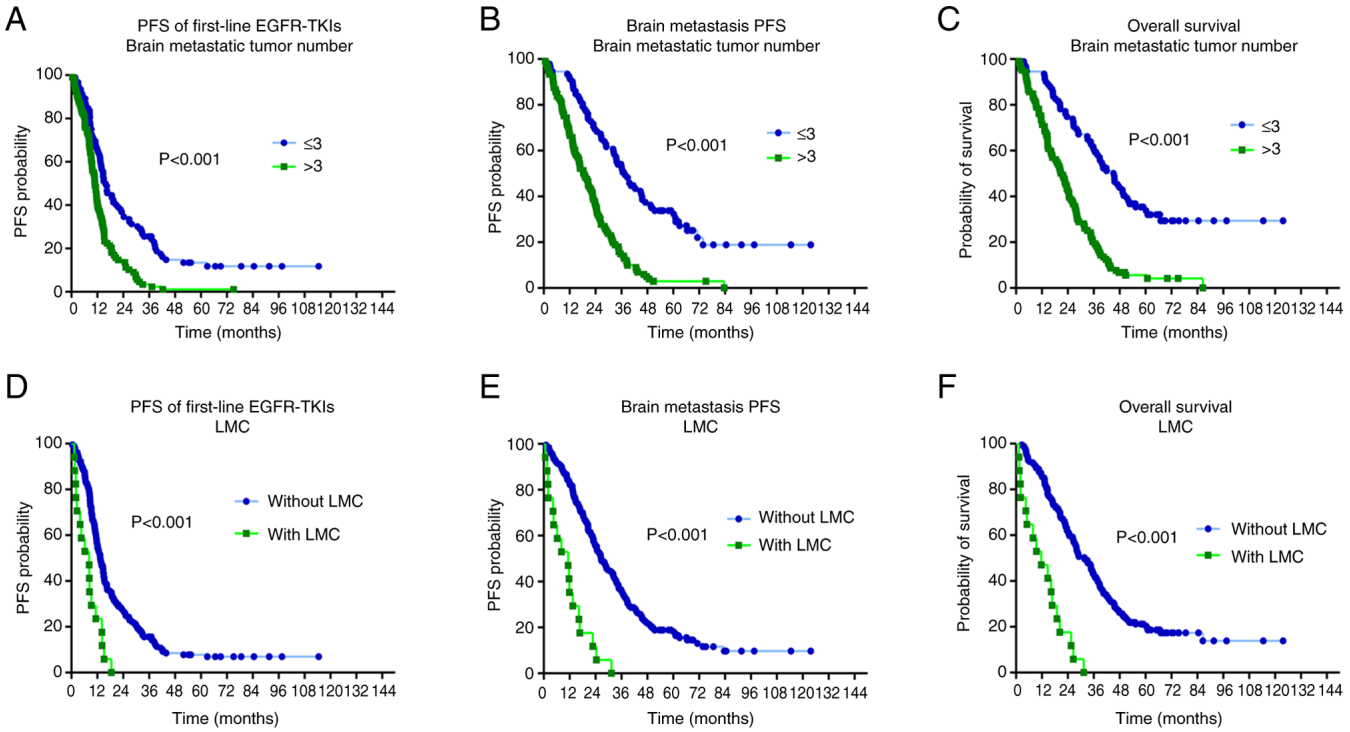

Figure 3. Analysis of PFS, brain metastasis PFS and OS using Kaplan-Meier survival curves based on brain metastatic number (≤3 and >3) and LMC status. Comparison of the median (A) PFS, (B) brain metastasis PFS and (C) OS between patients with different numbers of brain metastases. Comparison of the median (D) PFS, (E) brain metastasis PFS and (F) OS between patients with and without LMC. *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OS, overall survival; CI, confidence interval; LMC, leptomeningeal carcinomatosis.

osimertinib is not always affordable for patients or covered by a national insurance policy, although osimertinib has preferred efficacy and toxicity in the treatment of patients with advanced *EGFR*-mutated NSCLC (26,27).

To the best of our knowledge, the present study is the first to directly compare first- and second-generation EGFR-TKIs in untreated patients with *EGFR*-mutated NSCLC with baseline brain metastasis. The results revealed that afatinib was associated with a significantly longer median PFS than first-generation EGFR-TKIs (14.63 vs. 11.53 and 11.13 months). The assessment of the efficacy of EGFR-TKIs using PFS indicates systemic disease control, not only in the CNS. The results further demonstrated BMPFS and suggested that gefitinib, erlotinib and afatinib may have equal efficacy in controlling brain metastasis. The PFS of patients receiving first-line afatinib therapy was longer than that reported in a previous study by Huang *et al* (25) (10.9 months), in which 28 patients with baseline brain metastasis received afatinib, which was less than the number of patients included in the present study (n=93). In addition, information on local therapies such as radiation therapy or neurosurgery was not provided in the same study; therefore, these factors may have contributed to the differences between the two studies (25).

A greater number of intracranial metastatic tumors (>3) and the presence of LMC were identified as predictive factors associated with poor prognosis in the present study.

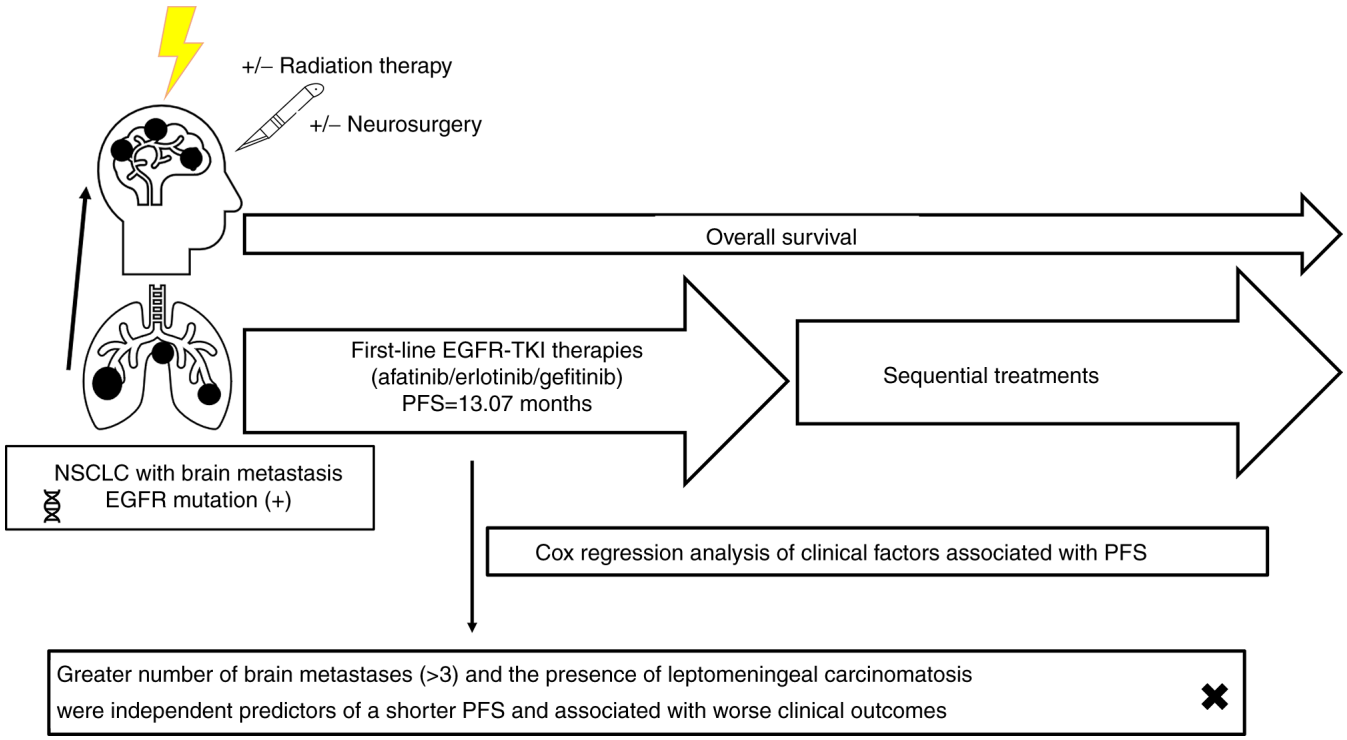

Figure 4. Conclusions of the present study. The present study identified that an increased number of brain metastases (>3) and the presence of LMC were independent predictors of a shorter PFS and associated with worse clinical outcomes in patients with *EGFR*-mutated NSCLC with baseline brain metastasis receiving first-line first- and second-generation EGFR-TKIs. *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OS, overall survival; LMC, leptomeningeal carcinomatosis; NSCLC, non-small cell lung cancer.

Patients with these two factors were also demonstrated to have significantly shorter BMPFS and OS times. According to the analysis of two previous studies, a greater number of intracranial metastatic tumors was reported to be associated with unfavorable outcomes in patients with NSCLC with brain metastasis (28,29). Leptomeningeal metastasis has been reported to be a severe complication in patients with advanced NSCLC in previous studies, and the appearance of LMC is associated with extremely poor prognosis (30,31). The life expectancy of patients with untreated LMC can be as short as 4-6 weeks (30,31). Although a greater number of intracranial metastatic tumors (>3) and the presence of LMC had been previously reported as clinical factors associated with poor clinical outcomes, the patients with NSCLC in the previous studies were non-selective and received heterogenous systemic treatment agents (28-31). In comparison with these previous studies, the patients included in the present study were specifically those with common *EGFR* mutations and baseline brain metastasis receiving first-line first- and second-EGFR-TKIs.

More therapeutic strategies for patients with NSCLC with unfavorable factors, such as more intracranial metastatic tumors or LMC, need to be developed and explored. For example, the anti-angiogenic agent bevacizumab in combination with EGFR-TKIs has been reported to increase the efficacy of controlling intracranial disease progression in previous studies (32,33). In patients with NSCLC with LMC, a recent study reported that the administration of the chemotherapy regimen pemetrexed intrathecally improved OS (31). In addition, third-generation osimertinib may be a preferred EGFR-TKI due to its improved efficacy regarding CNS penetration compared with first- and second-generation EGFR-TKIs in those with a greater number of intracranial metastatic tumors (>3) or the presence of LMC. Taken together, for patients with *EGFR*-mutated NSCLC with brain metastasis, the addition of bevacizumab and intrathecal pemetrexed to the regimen should be considered, and the choice of osimertinib can be considered for those with unfavorable outcomes.

Certain limitations of the present study should be mentioned and clarified. Firstly, the common *EGFR* mutations in the present study were exon 19 deletion and L858R, but no patients with major uncommon *EGFR* mutations, including G719X, S768I or L861Q, were included. The results of previous studies have demonstrated that second- and third-generation EGFR-TKIs are more effective than first-generation EGFR-TKIs in patients with advanced NSCLC harboring major uncommon EGFR mutations (G719X, S768I and L861Q) (4,34). Regarding the unequal efficacy of first- and second-generation EGFR-TKIs, patients with uncommon *EGFR* mutations were excluded from the present study. Secondly, the impact of the *de novo* T790M mutation on patients with NSCLC with baseline brain metastasis is unknown according to the results of the present study as no patients with this mutation were included. In addition, the efficacy of first-line osimertinib therapy was not assessed. Osimertinib has been conditionally reimbursed by the Taiwan Health Insurance Bureau since April 2020, and the timepoint of osimertinib reimbursement was later than the timepoint of inclusion in this study (4,35). Very few patients with advanced *EGFR*-mutated NSCLC in Taiwan received osimertinib as first-line therapy before national

reimbursement. This explains why those receiving first-line osimertinib were not included for analysis and comparison in the present study. Although osimertinib has been suggested as a preferred first-line therapy for advanced *EGFR*-mutated NSCLC, certain patients may experience intolerable toxicities induced by osimertinib which may require permanent discontinuation of osimertinib (36,37).

In the analysis of previous studies, patients with *EGFR*-mutated NSCLC with baseline brain metastasis were reported to have notably shorter PFS of EGFR-TKI treatments compared with those without brain metastasis (38,39). However, the previous studies did not report data on performing radiation therapies or neurosurgery in those patients with baseline brain metastasis (37,38). A previous study performed by Gu *et al* (40) reported that upfront brain radiation therapy in addition to first-line EGFR-TKIs improved intracranial disease control with a median BMPFS of 28.9 months. However, the systemic PFS of first-line EGFR-TKI treatments combined with upfront brain radiation therapy were not reported in the same previous study (39). The results of the present study are the first to demonstrate both systemic PFS and BMPFS in patients with *EGFR*-mutated NSCLC with baseline brain metastasis receiving first- and second-generation EGFR-TKIs, to the best of our knowledge. The median PFS of first-line EGFR-TKIs in the present study was 13.07 months with most patients receiving early brain radiation therapy, and the PFS of first-line EGFR-TKIs is in line with that reported by previous studies (6-10). Certain patients in the present study received salvage brain radiation therapy or neurosurgery, but no significant difference in PFS of first-line EGFR-TKIs was recorded between patients with and without salvage local therapies to brain metastasis. The analysis suggests that early brain radiation therapy may benefit the clinical outcomes of patients with *EGFR*-mutated NSCLC with baseline brain metastasis receiving first- and second-generation EGFR-TKIs. The results also indicate that for patients with *EGFR*-mutated NSCLC with baseline brain metastasis who are intolerant of osimertinib-related toxicities, first- and second-generation EGFR-TKIs combined with early local therapies are feasible therapeutic choices.

In conclusion, first- and second-generation EGFR-TKIs are effective and safe for treating untreated patients with *EGFR*-mutated NSCLC with baseline brain metastasis and remain feasible therapies if osimertinib is not available or if it causes intolerable toxicity. For patients whose unfavorable factors, such as a greater number of brain metastases and LMCs, are associated with worse clinical outcomes, combination therapeutic strategies and procedures should be considered.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CCH and PCH wrote and revised this manuscript. CTY, CCH, LCC and PCH were responsible for study conception and design. CCH, LCC, HWK, SCHK, JSJ and ACCH collected the data. HWK, CEW, SCHK, CTY and PCH provided the study materials and patients. CCH, LCC, CEW and CCW analyzed and interpreted the data. CCW and CTY confirm the authenticity of all the raw data. PCH, LCC and HWK supervised the study. All authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

The present retrospective study was approved by the Ethics Committee of Chang Gung Medical Foundation (approval no. 201901341A3). The study utilized the Chang Gung Research Database, and the Chang Gung Medical Foundation Ethics Committee granted a waiver of informed consent due to its retrospective nature. No identifiable data of the study patients, such as dates of birth or personal IDs, are presented in the present manuscript. The present study was performed in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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