Different Survival Benefit of Osimertinib in Different Sequences: A Real-World Outcome of Osimertinib Treatment in Pretreated T790M-Positive Advanced NSCLC in Taiwan

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Abstract

Background: To investigate the relationships among the clinical characteristics, different EGFR-TKIs, and osimertinib treatment in different treatment lines.

Methods: We retrospectively screened a total of 3807 patients diagnosed between 2013 and 2019 at Kaohsiung Chang Gung Memorial Hospital. Furthermore, 98 patients after re-biopsy or liquid with EGFR T790M mutation who received osimertinib were enrolled for analysis.

Results: Among all 98 patients, the median PFS of those who received osimertinib therapy was 10.48 months, and the median OS of those who received osimertinib therapy was 42.21 months. The OS of those who received osimertinib therapy after previous gefitinib, afatinib, or erlotinib therapy was 87.93, 49.00, and 42.00 months, respectively (P=0.006). There was a significant difference in disease control rate between those who received osimertinib treatment after previous chemotherapy (Group A) or immediately following EGFR-TKI therapy (Group B) (93.3% vs. 77.4%, P=0.029). There was also a significant difference in PS between those who received osimertinib as a second-line treatment and those who received it as a third-line treatment (10.83 vs. 17.33 months, P=0.044). In addition, COPD tended to be a poor prognostic factor for PFS and OS.

Conclusion: In this retrospective real-world analysis, it was determined that pretreatment with gefitinib and previous chemotherapy could affect the treatment outcomes of NSCLC patients treated with osimertinib. Furthermore, COPD tended to a poor prognostic factor for PFS and OS in such patients.

Background

Lung cancer is the cancer with high prevalence and high mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for about 80%-85% of all cases of lung cancer. According to the results of history and molecular biology tests, the treatment of lung cancer is personalized. Among various target oncogenes, epidermal growth factor receptor (EGFR) mutations are earliest and key genetic drivers of NSCLC. EGFR mutations are present in 10% of the Caucasian population, but in 40%-50% of the Asian population, including the population of Taiwan.[1-3] Previous clinical trials and studies have shown that compared with platinum-based chemotherapy regimens, EGFR-tyrosine kinase inhibitors (TKIs) produce better response rates and fewer adverse reactions. The objective response rate of the first and second generation EGFR-TKI is around between 60% and 80%, and the median progression-free survival (PFS) duration is around 10 to 13 months.[4-12] When these patients experienced disease progression (PD), newly acquired resistant EGFR p.Thr790Met (T790M) point mutations were developed in about 50%-70% of patients.[13-15] These acquired resistant mutations enhance the binding affinity of adenosine triphosphate to the EGFR kinase domain, thereby reducing the efficacy of the first and second generation EGFR-TKIs.

Osimertinib, a third-generation EGFR-TKI, was designed to and is active in non-small cell lung cancers harboring the EGFR T790M mutation.[16-19] Published reports of clinical trials have shown that

osimertinib has better efficacy in patients who undergo disease progression after the first and second-generation EGFR-TKI treatments.[16-19] AURA 3, a phase 3 clinical trial regarding osimertinib, also reported an better PFS associated in osimertinib compared to standard chemotherapy for NSCLC patients with acquired T790M mutations.[19] Therefore, re-biopsy or liquid biopsy is needed to prove the mechanism of acquired drug-resistance when EGFR mutations patients with PD after EGFR-TKI treatment.

In this study, we evaluated the response rate, progression-free survival (PFS), and overall survival (OS) of patients who received osimertinib treatment after a first-generation EGFR-TKI (gefitinib or erlotinib) or a second-generation EGFR-TKI (afatinib). The main objective of this study was to investigate the relationships among the clinical characteristics, different EGFR-TKIs, and osimertinib treatment in different treatment lines.

Methods

The study retrospectively screened a total of 3807 patients who were diagnosed with pathologically-confirmed lung cancer between January 2013 and April 2019 at Kaohsiung Chang Gung Memorial Hospital. Among these patients, there were 879 patients with inoperable EGFR mutation-positive adenocarcinoma who had received a first-generation EGFR-TKI (gefitinib or erlotinib) or a second-generation EGFR-TKI (afatinib) as the first-line therapy. Furthermore, 267 of these 879 patients who were resistant to first- or second-generation EGFR-TKIs had received a re-biopsy (including bronchoscopy, chest computed tomography guided biopsy, or video-assisted thoracoscopic surgery) and/or liquid biopsy (the Department of Pathology of Kaohsiung Chang Gung Memorial Hospital was in charged for the detection of the EGFR T790M mutation in cell-free plasma DNA) between March 2015 and December 2018. Of those patients, there were 98 patients with EGFR T790M mutation-positive adenocarcinomas who had received osimertinib therapy (80 mg per day) for at least 2 weeks since March 2016. Among these 98 patients, 91 patients were provided with treatment through the expanded access programs supported by AstraZeneca until the occurrence of disease progression or the unacceptable adverse effects. All of the 98 patients who received osimertinib treatment were enrolled for analysis.

Each of these 98 patients regularly received a chest CT scan in initially start of the osimertinib treatment and every three months thereafter to evaluate their tumor responses. Brain MRI imaging and Tc-99m MDP bone scans would also be performed if there were related symptoms. Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and disease control rate (DCR) were calculated to evaluate their efficacy. The PFS was calculated from the time of starting osimertinib until the time of radiological progression based on RECIST (according to the Response Evaluation Criteria in Solid Tumors) v1.121 or death; with censoring at the time of the last follow-up in the event which the patient was not disease progression. The ORR was defined as the percentage of patients who presented a complete response or partial response in the first follow-up image study after the starting osimertinib treatment, while the DCR was calculated as the percentage of patients who exhibited a complete

response, partial response, or stable disease. Furthermore, the duration of overall survival was calculated the duration from the starting osimertinib treatment until the patient expired.

Statistical analysis

Data (including age, sex, tumor size, nodal stage, EGFR mutation subtypes) were collected and analyzed by SPSS for Windows version 15.0. Quantitative variables are presented as averages ± standard deviations. Statistical significance of univariate analysis was determined by the Mann-Whitney U test for continuous variables and chi-square test for dichotomous variables.

The Kaplan–Meier method was used to estimate the PFS and OS. A Cox proportional hazards regression was also performed to evaluate the determinants of PFS and OS. Differences were considered significant when the *P*-value was <0.05.

Results

The demographic and clinical characteristics of the 98 patients with EGFR T790M mutation-positive adenocarcinomas who received osimertinib therapy are described in Table 1. All the patients had adenocarcinoma histology and were at the advanced stage. The mean age of the patients was 61.12 ± 10.97 (range 34-82) years, and there were 40 (40.8%) male patients and 58 (59.2%) female patients. The EGFR genotyping at the initial diagnosis showed Del 19 mutations in 54 (55.1%), L858R mutations in 41 (41.8%), Del 19 and T790M in one (1.0%), and L858R and T790M in two (2.0%) of these adenocarcinoma patients. All the patients were pretreated with EGFR-TKIs: 49 (50.0%), 27 (27.6%), and 22 (22.4%) received gefitinib, erlotinib, and afatinib respectively. The EGFR genotyping at the secondary (re-biopsy or liquid biopsy) diagnosis showed Del 19 combined with T790M in 55 (56.1%) patients and L858R combined with T790M in 43 (43.9%). The time interval between biopsies was 25.95±16.56 (1.33-99.10) months.

Forty-five (45.9%) patients received at least one cycle of chemotherapy between the previous EGFR-TKI and osimertinib. Osimertinib was received by 42 (42.9%), 23 (23.5%), and 33 (33.7%) patients as the second-line, third-line, and ≧ fourth-line treatment, respectively. Of the 98 patients, 52 (53.1%) had partial responses, 31 (31.6%) had stable diseases, and 15 (15.3%) experienced disease progression. The overall response rate was 53.1%, and the disease control rate was 84.7%. Among all 98 patients, the median PFS of osimertinib therapy was 10.48 months, and the median OS of osimertinib therapy was 42.21 months.

Table 2 shows the responses to osimertinib treatment after previous therapy with a different first-line EGFR-TKI. There was no significant difference in response rate to osimertinib after previous therapy between the patients treated with the different first-line EGFR-TKIs. The median PFS of those who received osimertinib therapy after previous therapy with gefitinib, afatinib, or erlotinib was 12.83, 11.87, and 10.90 months, respectively (P=0.293) (Supplementary Figure 1) . The median OS of those who received osimertinib therapy after previous therapy with gefitinib, afatinib, or erlotinib was 87.93, 49.00, and 42.00 months, respectively (Supplementary Figure 1); there was a significant difference in OS between the patients treated with the different first-line EGFR-TKIs (P=0.006).

Table 3 shows the response, PFS, and OS results of the patients who received osimertinib treatment after previous chemotherapy (Group A) or immediately following treatment with another EGFR-TKI (Group B). There was no significant difference in overall response rate between these two groups (62.2% vs. 45.3%, P=0.068), but there was a significant difference in disease control rate between these two groups (93.3% vs. 77.4%, P=0.029). There was no significant difference in PFS (12.17 vs. 10.83 months, P=0.362) or OS (54.27 vs. NA months, P=0.274) between these two groups.

Furthermore, we compared the response results for the patients treated with osimertinib as the second-line, third-line, or ≥ fourth-line therapy (Table 4). There was partial significant difference in median PFS between the patients treated with osimertinib as the second-line, third-line, or ≥ fourth-line therapy (10.83, 17.33, and 9.33 months, respectively, P=0.077) (Supplementary Figure 2), but there was a significant difference in median PFS between the patients treated with osimertinib as the second-line or third-line therapy (10.83 vs. 17.33 months, hazard ratio=0.51, 95% CI=0.26-0.99), P=0.044) (Supplementary Figure 3). There was no significant difference in OS among these patients.

Table 5 shows the subgroup analysis of PFS and OS. In terms of PFS, there were significant differences in the patients with a low BMI level (P=0.036, hazard ratio=0.56, 95% CI= 0.32-0.97) (Supplementary Figure 4), without COPD (P=0.011, hazard ratio=0.44, 95% CI= 0.23-0.84) (Supplementary Figure 5), and without brain metastasis before osimertinib treatment (Patients were without brain metastasis at the time osimertinib was initiated) (P=0.029, hazard ratio=0.56, 95% CI= 0.33-0.95) (Supplementary Figure 6). In terms of OS, there was a significant difference only in the patients without COPD (P=0.031, hazard ratio=0.45, 95% CI= 0.21-0.95). Using a Cox proportional hazards regression, we determined that brain metastasis before osimertinib treatment was a poor prognostic factor for PFS and that gefitinib as a first-line therapy and inclusion in Group A (osimertinib treatment after previous chemotherapy) were better prognostic factors for OS (Table 6). Furthermore, COPD tended to be a poor prognostic factor for PFS and OS (Table 6).

Discussion

In this study, we evaluated the response to osimertinib among NSCLC patients with T790M EGFR-resistant mutations following treatment with first- or second-generation EGFR-TKIs. We found that the gefitinib group had better OS (Table 2), that osimertinib treatment after previous chemotherapy (Group A) had a better response rate (Table 3), that osimertinib as the third-line treatment had better PFS than osmertinib as the second-line treatment (Table 4), that brain metastasis noted during osimertinib treatment was a poor prognostic factor for PFS, that gefitinib as a first-line therapy and inclusion in Group A (osimertinib treatment after previous chemotherapy) were better prognostic factors for OS, and that COPD tended to be a poor prognostic factor for PFS and OS (Table 6).

As shown in Table 7. In group A, 12 (26.67%) patients were with brain metastasis before osimertinib; the PFS was 11.07 months in patients with brain metastasis before osimertinib versus 21.13 months in patients without brain metastasis before osimertinib, respectively. In group B, 20 (37.7%) patients were

with brain metastasis before osimertinib; the PFS was 10.27 months in patients with brain metastasis before osimertinib versus 11.87 months in patients without brain metastasis before osimertinib, respectively. So, this could explain osimertinib as the third-line treatment had better PFS than osimertinib as the second-line treatment.

In the LUX-Lung 3 and LUX-Lung 6 trials, OS was significantly longer for patients with EGFR Del19-positive tumors in the afatinib group than in the chemotherapy group in both trials: in LUX-Lung 3, median OS was 33.3 months (95% CI = 26.8-41.5) in the afatinib group versus 21.1 months (16.3-30.7) in the chemotherapy group (HR = 0.54, 95% CI = 0.36-0.79, p=0.0015); in LUX-Lung 6, it was 31.4 months (95% CI = 24.2-35.3) versus 18.4 months (14.6-25.6), respectively (HR = 0.64, 95% CI = 0.44-0.94, p=0.023). By contrast, there were no significant differences by treatment group for patients with EGFR L858R-positive tumors in either trial. in LUX-Lung 3, median OS was 27.6 months (19.8-41.7) in the afatinib group versus 40.3 months (24.3-not estimable) in the chemotherapy group (HR = 1.30, 95% CI = 0.80-2.11, p=0.29); in LUX-Lung 6, it was 19.6 months (95% CI = 17.0-22.1) versus 24.3 months (19.0-27.0), respectively (HR 1.22, 95% CI 0.81-1.83, p=0.34). The absence of an effect in patients with L858R mutations suggests that EGFR Del19-positive disease might be distinct from EGFR L858R-positive disease[6, 20, 21]. This different EGFR-TKIs effect between Del19 and L858R could also explain why osimertinib as the third-line treatment had better PFS than osimertinib as the second-line treatment in our study. Furthermore, LUX-Lung 3 results suggested cisplatin plus pemetrexed promoted longer PFS in L858R patients (8.1 months) than in Del19 patients (5.6 months); another Japan study results also suggested cisplatin plus pemetrexed regimen may confer higher efficacy for L858R patients in second line or later settings[22]. These suggested that chemotherapy has better survival benefit in L858R-positive than Del19-positive. Table 8 showed the survival difference between L858R and Del19 in our study. In L858R-positive patients, group A and group B have a trend of significant difference in PFS (12.5 months versus 9.0 months, p=0.319); by contrast, in Del19-positive patients, group A and group B have no significant difference in PFS (15.70 months versus 11.93 months, p=0.950). The survival difference between L858R and Del19 could explain osimertinib as the third-line treatment (chemotherapy treated before osimertinib) had better PFS than osimertinib as the second-line treatment.

Following pretreatment with gefitinib, osimertinib tended to have a better PFS in this study (Table 2). This data was similar to that of another study from Taiwan[23] in which the PFS for patients treated with first-generation and second-generation EGFR-TKIs was 20.3 and 11.6 months, respectively (hazard ratio HR=0.40, 95% CI= 0.18-0.82, P=0.031)[23]. Kuo et al.[23] digital PCR was used in the re-biopsy of the tissues to determine the differences between the alleles frequencies of mEGFR (19del or L858R) (AF_{mEGFR}) and T790M (AF_{T790M}) after acquiring resistance between the first and second generation EGFR-treated. In Kuo's study, the AF_{T790M}/AF_{mEGFR} ratio of the first-generation EGFR-TKIs treatment group was significantly higher than that of the second-generation EGFR-TKIs treatment group. In addition, there was a highly significant correlation between AF_{T790M} and $AF_{mEGFR.}$ This could explain why osimertinib tended to have a better PFS following pretreatment with gefitinib than with afatinib in this study. In our

study, these data regarding AF_{T790M}/AF_{mEGFR} ratio was not available due to its retrospective study. So Kuo's data cannot explain a better PFS following pretreatment with gefitinib than with erlotinib.

In Taiwan, gefitinib (since November 2007) was covered by national reimbursement earlier than erlotinib (since June 2008) and afatinib (since May 2014). Furthermore, osimertinib was approved with second-line use since 2016 and first-line use since 2019, but covered by national reimbursement since April 2020 in Taiwan. The timing difference of approval and national reimbursement time difference could affect outcome between these three first-line EGFR-TKIs.

Compared with the first-generation EGFR-TKIs, the second-generation EGFR-TKI exhibits a broader inhibition spectrum and has an irreversible effect on the tyrosine kinases of EGFR and other ErbB family members.[24] Previous investigations[25-27] have shown that tumors are resistant to second-generation EGFR-TKIs usually show undetectable levels of EGFR and HER2 amplification, which may indicate a greater advantage of activating EGFR mutant clones in tumors. In contrast, in tumors that acquired resistance to the first-generation EGFR-TKI, EGFR and HER2 amplification were found at a consistent frequency,[13, 28] suggesting a less dominant place of EGFR-activating mutations in this scenario.

Previous studies Oxnard and Remon yielded controversial results that investigated the predictive role of the T790M allele in liquid biopsies examined the ratio of T790M to activating EGFR-mutation alleles.[29, 30] Oxnard et al.[29] showed that he ratio of T790M to activating EGFR mutations is related to the depth of response to osimertinib treatment, while this association was not noted by Remon et al.[30] in a similar study setting. Instead of liquid biopsy samples, our study showed that using tissue re-biopsies (liquid biopsy: tissue re-biopsy= 31.6%: 68.4%, Table 1) is feasible for determining the predictive role of the T790M allele.

In our study, there was a trend toward a significant difference in median PFS between the use of osimertinib as a second-line, third-line, or ≧ fourth-line therapy, and there was a significant difference in median PFS between the use of osimertinib as a second-line therapy or third-line therapy (Table 4). This PFS data was different from the data of another study from Taiwan[23] in which the hazard ratio was 1.03 (95% CI=0.44-2.20, P=0.941). Also, the PFS data in our study is different from the PFS data from the AURA II study[31]; in that study, the PFS for osimertinib as the second-line or third-line therapy was 11.0 (6.7-NR) and 12.4 (9.5-15.5) months, respectively. Furthermore, there was no significant difference in OS in both of these studies. Many related studies also describe the effects of using the second EGFR-TKI after the initial exposure [32-36]; furthermore, these previous studies described different results. During chemotherapy, the original EGFR-dependent cells may re-grow, and a second remission may be obtained by introducing EGFR-TKIs after chemotherapy. In addition to sensitivity to acquired T790M mutations, osimertinib is also sensitive to original EGFR mutations (Del 19 and L8585R)[16]. This hypothesis may explain the higher RR and DCR seen in this study (Table 3) as compared with other study results for second-round EGFR-TKIs of different designs[32-35].

To detect T790M resistance mutations, in most studies, re-biopsy was performed when the disease progressed[13, 37], and the results showed that T790M accounted for 50-60% of the resistance mechanism. Since the cancer genome is heterogeneous, it can evolve over time, and it can also interact with different treatments[38], It is unclear whether the timing of a re-biopsy or liquid biopsy will affect the detection rate of T790M. However, in one previous study[39], The results provide evidence that there is no significant association between the timing of re-biopsy and the detection rate of T790M. In addition, this study also shows that T790M can exist for a long time after the progression of EGFR-TKI treatment, and it is also an important carcinogenic driving factor. In our study, the time interval between biopsies was 25.95±16.56 (1.33-99.10) months (Table 1); furthermore, the patients treated with gefitinib had a longer time interval between biopsies than those for the patients treated with erlotinib and afatinib. As previous description, gefitinib (since November 2007) was covered by national reimbursement earlier than erlotinib (since June 2008) and afatinib (since May 2014) in Taiwan. So, this could explain why the gefitinib group had a longer PFS than the erlotinib and afatinib groups. Furthermore, osimertinib was approved with second-line use since 2016 and first-line use since 2019, but covered by national reimbursement since April 2020. The timing difference of approval and national reimbursement time difference could affect outcome between these three first-line EGFR-TKIs.

Non-small cell lung cancer is the main cause of brain metastases.[40, 41] Amongst these with recurrent/advanced NSCLC, brain metastases are a common cause for cancer-related morbidity and mortality. As targeted therapy continues to improve the prognosis of NSCLC patients with target oncogene,[8] The deterrence of brain metastases has become an increasingly relevant treatment problem. The first and second generation EGFR-TKIs (ie gefitinib, erlotinib, and afatinib) cannot effectively cross the intact complete blood-brain barrier which the ratio of the patient's cerebrospinal fluid to plasma is as low as 0.01 to 0.003. In the AURA 3 and FLAURA studies[19, 42], the PFS benefit of osimertinib was observed in patients with or without known or treated brain metastases at trial entry. Patients with brain metastases tended to have a worse PFS benefit (PFS = 15.2, 95% CI = 12.1–21.4 months) than those without brain metastases (PFS =19.1, 95% CI = 15.2–23.5 months) in EGFR mutation NSCLC patients in the FLAURA study[42]. It seems that this could explain why initial brain metastasis did not influence the osimertinib PFS but brain metastasis during osimertinib treatment did influence the osimertinib PFS in our study.

This retrospective study has several limitations. First, this study was conducted at a single medical center, such that the patient population may be biased by patient selection and referral patterns. Second, this study was a retrospective survey, which not only resulted in incomplete data for some patients, but also did not control for laboratory examinations. Third, the multiple lines of treatment before administering osimertinib may have confounded the effects. Another limitation was that any genomic alterations beyond EGFR mutations were not measured in this study. Only first-generation EGFR-TKIs were enrolled for analysis in AURA 3 trial. Although both first- and second-generation EGFR-TKIs were enrolled for analysis, but it still is a retrospective analysis. In the future, further randomized controlled trial should be conducted to evaluate PFS and OS benefit between different sequences of EKFR-TKIs.

Conclusion

We found that the gefitinib group had better OS, that osimertinib treatment after previous chemotherapy (Group A) had a better response rate, that osimertinib as the third-line treatment had a better PFS than osimertinib as the second-line treatment, that brain metastasis noted before osimertinib treatment was a poor prognostic factor for PFS, that gefitinib as a first-line treatment and inclusion in Group A (osimertinib treatment after previous chemotherapy) were better prognostic factors for OS, and that COPD tended to be a poor prognostic factor for PFS and OS. But, osimertinib is still neither easily available nor covered by national reimbursement in many countries. In our study, an alternative sequence (using chemotherapy first when initially osimertinib not available) still s better PFS benefit. Furthermore,

Abbreviations

COPD: chronic obstructive pulmonary disease

DCR: disease control rate

EGFR: epidermal growth factor receptor

NSCLC: non-small cell lung cancer

ORR: overall response rate

OS: overall survival

PD: disease progression

PFS: progression-free survival

RECIST: Response Evaluation Criteria in Solid Tumors

TKIs: tyrosine kinase inhibitors

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the requirements for patient consent were waived (IRB: 201901263B0).

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Competing interests statement

The authors state that that there no potential conflicts of interest.

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Availability of data and materials

The datasets analyzed during the current study would be available from the corresponding author on reasonable request.

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Tables

Table 1. Demographic and clinical characteristics of all patients. (n=98)

Sex	Male	40 (40.8%)
	Female	58 (59.2%)
Age (in years)		61.12±10.97 (34-82)
>65		35 (35.7%)
≤65		63 (64.3%)
BMI		24.45±3.49 (16.24-33.06)
Tumor size (in cm) N=63		4.30±2.17 (0.8-15.0)
Stage	IIIA	1 (1.1%)
	IIIB	2 (3.2%)
	IV	95 (95.9%)
First EGFR mutation test	Del 19	54 (55.1%)
	L858R	41 (41.8%)
	Del 19 & T790M	1 (1.0%)
	L858R & T790M	2 (2.0%)
Second EGFR mutation test	Del 19 & T790M	55 (56.1%)
	L858R & T790M	43 (43.9%)
ECOG	0	29(29.6%)
	1	67 (68.4%)
	2	2(2.0%)
	3-4	0 (0%)
Comorbidities	DM	9 (9.2%)
	COPD	12 (12.2%)
	Hypertension	23 (23.5%)
Smoking status	Never	77 (78.6%)
	Ever	12 (12.2%)
	Current	9 (9.2%)
CEA level	≤ 5	33 (33.7%)
	> 5	65 (66.3%)

Diagnosis at first presentation	Bronchoscopy	41 (41.8%)
	CT-guide	21 (21.4%)
	Operation	20 (20.4%)
	Pleural effusion	15 (15.3%)
	LN aspiration	1 (1.0%)
Diagnosis at second presentation	Bronchoscopy	10 (10.2%)
	CT-guide	18 (18.4%)
	Operation	23 (23.5%)
	Pleural effusion	16 (16.3%)
	Plasma DNA	31 (31.6%)
Time interval between biopsies (in months)	25.95±16.56 (1.33-99.10)	
First-line therapy	Geftinib	49 (50.0%)
	Erlotinib	27 (27.6%)
	Afatinib	22 (22.4%)
Osimertinib therapy	Second line	42 (42.9%)
	Third line	23 (23.5%)
	≧Fourth line	33 (33.7%)
Chemotherapy of at least one cycle between previous EGFR-TKI and osimertinib	45 (45.9%)	
Interval between 2 TKIs*	9.22±7.31 (0.87-27.23)	
Interval between 2 TKIs**	4.68±6.83 (0-27.23)	
Osimertinib response	CR	0 (0%)
	PR	52 (53.1%)
	SD	31 (31.6%)
	PD	15 (15.3%)
Death	43 (43.9%)	
Osimertinib therapy failure	65 (66.3%)	
Osimertinib therapy PFS total (median, in months)	10.48	
OS (median, in months)	42.21	

* Excluding the data of osimertinib use immediately after previous EGFR-TKI therapy (n=53, Group B).

** All patients (n=98).

Table 2. Response to osimertinib treatment after previous therapy with a different first-line EGFR-TKI (n=98).

GROUP	*Geftinib (n=49, 50.0%)*	*Afatinib (n=22, 22.4%)*	*Erlotinib (n=27, 27.6%)*	*P-value*
PR	29 (59.2%)	9 (40.9%)	14 (51.9%)	0.673
SD	14 (28.6%)	9 (40.9%)	8 (29.6%)	
PD	6 (12.2%)	4 (18.2%)	5 (18.5%)	
PFS (in months)	12.83	11.87	10.90	0.293
OS (in months)	87.93	49.00	42.00	0.006

Pearson's chi-squared test.

PR= partial response, SD= stable disease, PR= progression disease.

PFS= median progression free survival, OS= median overall survival.

Table 3. Response, PFS, and OS of the patients who received osimertinib treatment after previous chemotherapy (Group A) or immediately following treatment with another EGFR-TKI (Group B). (n=98)

GROUP	*After Chemotherapy (Group A) (n=45, 45.9%)*	*After Another EGFR-TKI (Group B) (n=53, 54.1%)*	*P-value*
PR	28 (62.2%)	24 (45.3%)	0.068
SD	14 (31.1%)	17 (32.1%)	
PD	3 (6.7%)	12 (22.6%)	
DCR	42 (93.3%)	41 (77.4%)	0.029
PD	3 (6.7%)	12 (22.6%)	
PFS (in months)	12.17	10.83	0.362*
OS (in months)	54.27	NA	0.274**
Pearson's chi-squared test.			
PR= partial response, SD= stable disease, PR= progression disease, DCR= disease control rate. PFS= median progression free survival, OS= median overall survival.			
*PFS Hazard Ratio: 0.80 (0.49-1.30). **OS Hazard Ratio: 1.40 (0.76-2.58).			

Table 4. OS and PFS of T790M-mutated lung adenocarcinoma patients treated with osimertinib as second-line, third-line or ≥ fourth-line therapy. (n=98)

GROUP	*Second-line (n=42, 42.9%)*	*Third-line (n=23, 23.5%)*	*≥ Fourth-line (n=33, 33.7%)*	*P-value*
Between 2nd, 3rd, & ≥4th line				
PFS (in months)	10.83	17.33	9.33	0.077
OS (in months)	N/A	N/A	54.27	0.431
Between 2nd & 3rd line				
PFS (in months)	10.83	17.33		0.044*
OS (in months)	N/A	N/A		0.740**
PFS= median progression free survival, OS= median overall survival.				
*PFS Hazard Ratio: 0.51 (0.26 -0.99). **OS Hazard Ratio: 1.16 (0.49 -2.74).				

Table 5. Median of PFS and OS of T90M-mutated lung adenocarcinoma patients. (Subgroup analysis) (n=98)

GROUP			*P-value*	*Hazard Ratio (95%CI)*
Months after receiving a previous EGFR-TKI	**<1month (n=48, 49.0%)**	**≥1month (n=50, 51.0%)**		
PFS (in months)	10.30	13.17	0.109	0.67 (0.41 -1.10)
OS (in months)	67.10	56.37	0.930	1.03 (0.56 -1.90)
BMI level	**<27 (n=76, 77.6%)**	**≥ 27 (n=22, 22.4%)**		
PFS (in months)	13.10	9.25	0.036	0.56 (0.32 -0.97)
OS (in months)	61.20	42.00	0.192	0.64 (0.33 -1.25)
CEA level	**≤ 5 (n=33, 33.7%)**	**>5(n=65, 66.3%)**		
PFS (in months)	12.07	12.13	0.901	0.97 (0.57 -1.63)
OS (in months)	59.27	61.00	0.987	0.99 (0.53 -1.87)
DM	**Without (n=89, 90.8%)**	**With (n=9, 9.2%)**		
PFS (in months)	12.43	10.90	0.739	0.87 (0.37 -2.01)
OS (in months)	59.27	46.43	0.827	0.90 (0.35 -2.31)
HTN	**Without (n=75, 76.5%)**	**With (n=23, 23.5%)**		
PFS (in months)	12.07	10.90	0.544	1.20 (0.66 -2.17)
OS (in months)	54.27	87.93	0.334	1.44 (0.68 -3.03)
COPD	**Without (n=86, 87.8%)**	**With (n=12, 12.2%)**		
PFS (in months)	12.43	5.89	0.011	0.44 (0.23 -0.84)
OS (in months)	61.20	38.52	0.031	0.45 (0.21 -0.95)

GROUP			*P-value*	*Hazard Ratio (95%CI)*
Initial Brain Metastasis	**Without (n=84, 85.7%)**	**With (n=14, 14.3%)**		
PFS (in months)	12.43	11.00	0.347	0.71 (0.35 -1.45)
OS (in months)	61.00	59.27	0.235	0.63 (0.29 -1.36)
Brain Metastasis (osi)	**Without (n=66, 67.3%)**	**With (n=32, 32.7%)**		
PFS (in months)	13.87	10.90	0.029	0.56 (0.33 -0.95)
OS (in months)	66.53	47.90	0.088	0.59 (0.32 -1.09)
PFS= median progression free survival, OS= median overall survival. DM= Diabetes Mellitus, HTN= Hypertension, Brain Metastasis (OSI) = brain metastasis was noted before osimertinib treatment.				

Table 6. Cox regression analysis: effects of potential prognostic factors on PFS and OS for T790M-mutated lung adenocarcinoma.

		Progression-Free Survival		*Overall Survival*	
Prognostic Factor	*Classification*	*Hazard Ratio*	*P-Value*	*Hazard Ratio*	*P-Value*
First-Line Drug	Afatinib vs. Erlotinib	1.02 (0.47 -2.22)	0.959	0.97 (0.37 -2.56)	0.953
First-Line Drug	Geftinib vs. Erlotinib	0.79 (0.42 -1.47)	0.452	0.30 (0.14 -0.66)	0.003*
Group	A vs. B	3.24 (0.72 -14.7)	0.127	13.7 (1.39 - 135)	0.025*
Months after receiving a previous EGFR-TKI	≥one month vs. <one month	0.33 (0.08 -1.27)	0.107	0.12 (0.01 -1.10)	0.061
Osimertinib Line Drug	Third line vs. Second line	0.50 (0.20 -1.26)	0.145	0.67 (0.21 -2.16)	0.507
Osimertinib Line Drug	Fourth line vs. Second line	1.00 (0.47 -2.14)	0.996	1.01 (0.39 -2.65)	0.977
BMI	BMI<27 vs. BMI ≥27	0.68 (0.36 -1.29)	0.237	0.73 (0.32 -1.65)	0.451
CEA level	≤ 5 vs. >5	0.98 (0.54 -1.78)	0.944	1.03 (0.50 -2.13)	0.939
Smoking	Never vs. Current	0.97 (0.41 -2.26)	0.935	1.04 (0.39 -2.80)	0.932
Smoking	Experienced vs. Current	0.95 (0.32 -2.82)	0.922	0.56 (0.13 -2.35)	0.427
Diabetes Mellitus	No vs. Yes	0.66 (0.25 -1.72)	0.391	0.67 (0.20 -2.22)	0.512
Hypertension	No vs. Yes	1.15 (0.59 -2.24)	0.690	1.67 (0.69 -4.06)	0.255
Initial Brain Metastasis	No vs. Yes	1.15 (0.46 -2.90)	0.767	0.81 (0.28 -2.34)	0.703
Brain Metastasis (OSI)	No vs. Yes	0.50 (0.26 -0.99)	0.045*	0.52 (0.21 -1.28)	0.155
COPD	No vs. Yes	0.48 (0.23 -1.00)	0.051	0.40 (0.16 -1.01)	0.052

PFS= median progression free survival, OS= median overall survival. Group A= osimertinib treatment after previous chemotherapy, Group B= osimertinib treatment immediately following treatment with another EGFR-TKI. Brain Metastasis (OSI) = brain metastasis was noted before osimertinib treatment.

Table 7. PFS and OS of the patients who received osimertinib treatment after previous chemotherapy (Group A) or immediately following treatment with another EGFR-TKI (Group B). Brain metastasis before osimertinib subgroup analysis. (n=98)

In group A

Brain metastasis (OSI)	NO	YES	P value
Total n=45	33 (73.3%)	12 (26.67%)	
PFS (months)	21.13	11.07	0.113
OS (months)	56.37	41.27	0.010

In group B

Brain metastasis (OSI)	NO	YES	P value
Total n=53	33 (62.3%)	20 (37.7%)	
PFS (months)	11.87	10.27	0.091
OS (months)	NA	67.10	0.340

Brain Metastasis (OSI) = brain metastasis was noted before osimertinib treatment.

Table 8. PFS and OS of the patients who received osimertinib treatment after previous chemotherapy (Group A) or immediately following treatment with another EGFR-TKI (Group B). L858R and Del 19 subgroup analysis. (n=95)

Group n=95	After Chemotherapy (Group A) (n=42, 44.2%)	After Another EGFR-TKI (Group B) (n=53, 55.8%)	P value
L858R	15 (35.7%)	26 (49.1%)	0.192
Del 19	27 (64.3%)	27 (50.9%)	
L858R n=41	15	26	
PFS (months)	12.5	9.0	0.319
OS (months)	66.53	67.10	0.994
Del 19 n=54	27	27	
PFS (months)	15.70	11.93	0.950
OS (months)	56.37	NA	0.232
Total n=95	42	53	
PFS (months)	13.17	10.83	0.315
OS (months)	56.37	NA	0.407
Data had exclude the double mutation with T790M if first biopsy. PFS= median progression free survival, OS= median overall survival.			

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