Original Article



# The relationship between preliminary efficacy and prognosis after first-line *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI) treatment of advanced non-small cell lung cancer

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**Background:** Nowadays, patients with *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI)-sensitive advanced non-small cell lung cancer (NSCLC) receive *EGFR*-TKIs as first-line treatment. We aimed to analyze the relationship between preliminary efficacy (tumor shrinkage within 1 month) and progression-free survival (PFS) after first-line *EGFR*-TKI treatment.

**Methods:** A total of 82 patients with *EGFR*-TKI-sensitive advanced NSCLC confirmed by histopathology from January 2013 to January 2017 were retrospectively analyzed. All patients received first-line *EGFR*-TKI treatment and follow-up at Shanghai Chest Hospital.

**Results:** Of a total of 82 patients, 42 (51.2%) patients achieved partial response (PR) within 1 month, and 40 (48.8%) patients achieved stable disease (SD: −30% to 0) within 1 month. The median PFS among all patients was 10 months. The median PFS in patients achieving PR within 1 month was 10.0 months. The median PFS in patients achieving SD (−30% to 0) within 1 month was 9.3 months. There was no statistically significant difference between PR within 1 month and SD (−30% to 0) within 1 month (P=0.620). In the *EGFR*-sensitive mutation subgroup, there was also no statistically significant difference between PR within 1 month and SD (−30% to 0) within 1 month. Univariate and multivariate analysis of first-line *EGFR*-TKI treatment showed that age, *EGFR* mutation type, and T staging had effects on PFS. Patients who were more than 65 years old, had *EGFR* 19del mutation, along with a T staging less than 4, had a longer PFS; these differences were statistically significant. Liver metastasis, bone metastasis, and brain metastasis were not shown to be related to PFS.

**Conclusions:** For patients with *EGFR*-TKI-sensitive advanced NSCLC, there is no correlation between preliminary efficacy (tumor shrinkage within 1 month) and PFS after first-line *EGFR*-TKI treatment.

**Keywords:** Non-small cell lung cancer (NSCLC); *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI); first-line treatment; preliminary efficacy; progression-free survival (PFS)

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## Introduction

Lung cancer is a malignant tumor with the highest morbidity and mortality both worldwide and within China. According to the 2015 statistics (1), there were a total of 733,000 new cases of lung cancer in China, and the total number of deaths was about 610,000 (male: 432,400, female: 177,800). NSCLC accounts for 85–90% of all diagnosed lung cancers. About 70% of patients are at an advanced stage when initially diagnosed. For patients with advanced non-small cell lung cancer (NSCLC), the efficacy of traditional platinum-based chemotherapy and radiotherapy has plateaued; thus, the overall survival (OS) of most patients is not satisfactory (2).

In recent years, molecular-targeted therapy for lung cancer driver genes has progressed rapidly. The proportion of driver mutations in the *EGFR* tyrosine kinase region is 15–40%, which is particularly prevalent in Asians, females, and non-smokers or mild smokers with NSCLC (3-6). More than 90% of known *EGFR* driver mutations are 19del or 21L858R (7,8). With the ongoing series of large-scale clinical trials (9-11), recent data have revealed that first-line targeted therapy for advanced NSCLC with *EGFR*-sensitive mutation shows a higher response rate and a longer PFS compared with chemotherapy, and the median PFS is about 10–12 months. Thus, *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib and erlotinib have been widely used for first-line treatment, while in China icotinib has been mainly approved for clinical use. Clinically, we have observed that some patients have rapid tumor shrinkage at the initial stage of first-line *EGFR*-TKI treatment, but some patients have slower tumor shrinkage. It remains unknown whether different preliminary efficacy is related to PFS. In our study, we aimed to analyze the relationship between preliminary efficacy (tumor shrinkage within 1 month) and PFS after first-line *EGFR*-TKI treatment.

## Methods

### *Patients*

We identified and reviewed the clinical data of patients who were diagnosed with NSCLC at Shanghai Chest Hospital from January 2013 to January 2017. The study protocol was approved by the Ethics Committee of Shanghai Chest Hospital [KS(Y)1708] and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Due to the retrospective nature of this study, the need for informed consent was waived. The inclusion criteria were as follows: (I) patients with stage IIIb/IV NSCLC (NSCLC staging was performed according to the 7$^{th}$ edition of the TNM classification); (II) patients whose tumors were positive for *EGFR*-sensitive mutation such as exon 19 deletion or 21L858R point mutation [the Amplification Refractory Mutation System (ARMS) was used to detect mutations in the *EGFR* gene]; (III) patients who had responded to first-line *EGFR*-TKI treatment without the resistance mutation. The baseline clinical characteristics included age at diagnosis, tumor histology, smoking status, gender, etc.

### *Clinical assessments*

Patients were given 150 mg of erlotinib daily or 250 mg of gefitinib daily, while another group of patients who were treated with icotinib received 125 mg three times daily. Clinical follow-up exams included a physical examination, an imaging examination, and laboratory tests, which were performed every 4 weeks. Efficacy was evaluated every month according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). We defined the response of the first month as preliminary efficacy. Patients who achieved PR within 1 month and SD (–30% to 0) within 1 month were analyzed in our study. If first-line treatment failed, second-line treatment would be given. All patients were regularly followed up after receiving targeted therapy in Shanghai Chest Hospital. The clinical data were complete and traceable. The follow-up ended on February 5$^{th}$, 2018. The PFS was calculated from the date of initiation of *EGFR*-TKIs to the date of disease progression or the last follow-up visit.

### *ARMS method*

DNA was extracted from five serial slices of a 5-μm paraffin section using the DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). PCR was performed, and the results were analyzed according to the manufacturer's protocol of the DxS *EGFR* mutation test kit (DxS) (12).

### *Statistical analysis*

SPSS22.0 statistical software (IBM, Armonk, NY, USA) was used for data processing. PFS was analyzed with the Kaplan-

 

Meier method. Single factor analysis and Cox multivariate regression analysis were used to explore the significant factors of survival. A P value of <0.05 was considered as statistically significant.

## Results

### *Patient characteristics*

A total of 82 patients with *EGFR*-TKI-sensitive advanced NSCLC confirmed by histopathology from January 2013 to January 2017 were retrospectively analyzed. Seventy-five (91.5%) patients were adenocarcinoma, and 7 (8.5%) patients were non-adenocarcinoma. Patients underwent *EGFR* mutation test by ARMS method, and 50 (61.0%) patients had *EGFR* 19del mutation while 32 (39.0%) patients had *EGFR* 21L858R mutation. Forty-two (51.2%) patients achieved PR within 1 month, and 40 (48.8%) patients achieved SD (–30% to 0) within 1 month. Demographic data of all patients are shown in *Table 1*.

### *Progression-free survival (PFS)*

The median PFS among all patients was 10 months (*Figure 1*). Among the total patients, the median PFS in patients achieving PR within 1 month was 10.0 months, and the median PFS in patients achieving SD (–30% to 0) within 1 month was 9.3 months (*Table 1*). There was no statistically significant difference between PR within 1 month and SD (–30% to 0) within 1 month (P=0.620) (*Figure 2*). In the *EGFR* 19del mutation subgroup, the median PFS in patients achieving PR within 1 month and achieving SD (–30% to 0) within 1 month was 10.8 and 12.0 months, respectively. A statistically significant difference was not found (P=0.829) (*Figure 3*). In the *EGFR* 21L858R mutation subgroup, the median PFS in patients achieving PR within 1 month and achieving SD (–30% to 0) within 1 month was 7.8 and 8.5 months, respectively. A statistically significant difference was also not found (P=0.206) (*Figure 4*).

### *Univariate and multivariate analysis*

Univariate and multivariate analysis of first-line *EGFR*-TKI treatment showed that age, *EGFR* mutation type, and T staging had effects on PFS. Patients who were more than 65 years old, had *EGFR* 19del mutation, along with a T staging less than 4, had a longer PFS; these differences were statistically significant. Liver metastasis, bone metastasis, and brain metastasis were not shown to be related to PFS (*Table 1*).

## Discussion

For *EGFR*-TKI-sensitive advanced NSCLC, first-line *EGFR*-TKI treatment has been established as the standard therapy. According to a study, patients who achieved PR/CR after *EGFR*-TKI treatment had a significantly longer survival than those achieved SD (13). However, the definition of SD according to RECIST criteria is too broad to predict prognosis. It can only be broadly divided into tumor enlargement of less than 20% and tumor regression of less than 30%. Another study evaluated the correlation between efficacy of targeted therapy and prognosis in previously treated advanced NSCLC; longer PFS and OS have been observed in SD (–30% to 0) patients when compared with SD (0 to +20%) patients (14). Clinically, we observed that some patients have rapid tumor shrinkage at the initial stage of first-line *EGFR*-TKI treatment, but some patients have slower tumor shrinkage. It remains unknown whether different preliminary efficacy is related to PFS. Our retrospective analysis found that there was no significant difference in PFS between PR within 1 month and SD (–30% to 0) within 1 month. This suggests that slow and rapid tumor shrinkage at the initial stage of first-line *EGFR*-TKI treatment could achieve a similar benefit to PFS. A study showed that for patients with *EGFR* mutation who achieved CR/PR after *EGFR*-TKI treatment, the median time to this efficacy was 4.2 weeks (95% CI: 3.9–4.5 weeks), and time to response was not related to PFS or OS in such patients (13). In another similar study, the PFS showed no significant difference in patients who achieved PR with or without early response (15). Some investigators reported that not only could the responsive patients obtain survival benefit, but those SD patients with tumor regression could as well (14). Another study examined individual patient-level data from five randomized trials (EURTAC, IPASS, ENSURE, LUX-Lung 3, and LUX-Lung 6) to assess whether the depth of response at 6 or 12 weeks could be used as a surrogate for PFS or OS, and the conclusion was that it could not (16). These results may support our conclusion, but these studies included patients with previous chemotherapy, and it remains unclear whether chemotherapy has effects on the response or PFS of *EGFR*-TKI treatment. The sample size is not very large in our study, which may be a limitation.

**Table 1** The relationship between clinical characteristic and prognosis among all patients

| Characteristic | N (%) | Median PFS (months) | Univariate analysis (P value) | Multivariate analysis [P value, HR (95% CI)] |
|---|---|---|---|---|
| Gender | | | 0.177 | – |
| Male | 41 (50.0) | 10.3 | | |
| Female | 41 (50.0) | 9.1 | | |
| Age, years | | | 0.010 | 0.005, 0.476 (0.285–0.975) |
| <65 | 51 (62.2) | 8.0 | | |
| ≥65 | 31 (37.8) | 13.3 | | |
| Histology | | | 0.842 | – |
| Adenocarcinoma | 75 (91.5) | 10.1 | | |
| Non-adenocarcinoma | 7 (8.5) | 8.3 | | |
| Smoker | | | 0.992 | – |
| No | 60 (73.2) | 10.1 | | |
| Yes | 22 (26.8) | 8.5 | | |
| Stage | | | 0.646 | – |
| IIIb | 13 (15.9) | 7.3 | | |
| IV | 69 (84.1) | 10.3 | | |
| *EGFR* mutation | | | 0.008 | 0.017, 1.82 (1.111–2.986) |
| 19del | 50 (61.0) | 11.0 | | |
| 21L858R | 32 (39.0) | 7.8 | | |
| Response to *EGFR*-TKIs | | | 0.620 | – |
| PR within 1 month | 42 (51.2) | 10.0 | | |
| SD (–30% to 0) within 1 month | 40 (48.8) | 9.3 | | |
| Drug | | | 0.420 | – |
| Gefitinib | 41 (50.0) | 10.2 | | |
| Erlotinib | 12 (14.6) | 7.4 | | |
| Icotinib | 29 (35.4) | 10.3 | | |
| Type | | | 0.478 | – |
| Central | 11 (13.4) | 12.0 | | |
| Peripheral | 71 (86.6) | 9.1 | | |
| T stage | | | 0.000 | 0.001, 2.49 (1.435–4.328) |
| <T4 | 55 (67.0) | 12.4 | | |
| T4 | 27 (33.0) | 7.6 | | |
| N stage | | | 0.628 | – |
| <N3 | 61 (74.4) | 9.3 | | |
| N3 | 21 (25.6) | 10.1 | | |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Characteristic | N (%) | Median PFS (months) | Univariate analysis (P value) | Multivariate analysis [P value, HR (95% CI)] |
|---|---|---|---|---|
| ECOG PS score | | | 0.439 | – |
| 0–1 | 78 (95.1) | 9.1 | | |
| ≥2 | 4 (4.9) | 14.2 | | |
| Metastatic sites | | | 0.155 | – |
| No | 13 (15.9) | 7.8 | | |
| Intrathoracic | 32 (39.0) | 13.3 | | |
| Extrathoracic | 37 (45.1) | 9.3 | | |
| Number of metastatic sites | | | 0.417 | – |
| 0 | 13 (15.9) | 7.8 | | |
| 1 | 31 (37.8) | 13.0 | | |
| ≥2 | 38 (46.3) | 10.0 | | |
| Liver metastasis | | | 0.199 | – |
| No | 76 (92.7) | 10.1 | | |
| Yes | 6 (7.3) | 7.4 | | |
| Bone metastasis | | | 0.379 | – |
| No | 58 (70.7) | 9.1 | | |
| Yes | 24 (29.3) | 10.0 | | |
| Brain metastasis | | | 0.674 | – |
| No | 66 (80.5) | 10.0 | | |
| Yes | 16 (19.5) | 8.4 | | |

ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*-TKI, *EGFR* tyrosine kinase inhibitor; HR, hazard ratio; PFS, progression-free survival; PR, partial response; SD, stable disease (tumor shrinkage: –30% to 0).

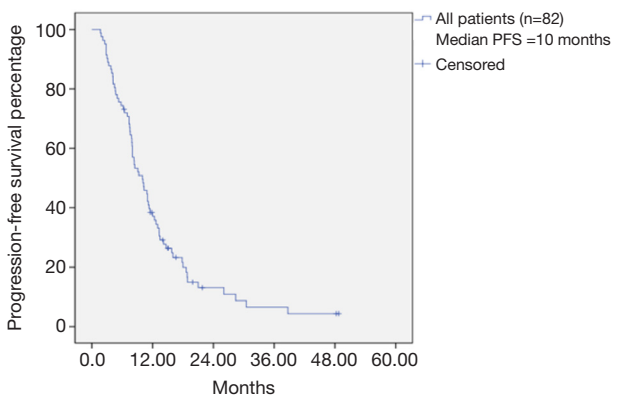


**Figure 1** Kaplan-Meier survival curve for PFS analysis among all patients. PFS, progression-free survival.

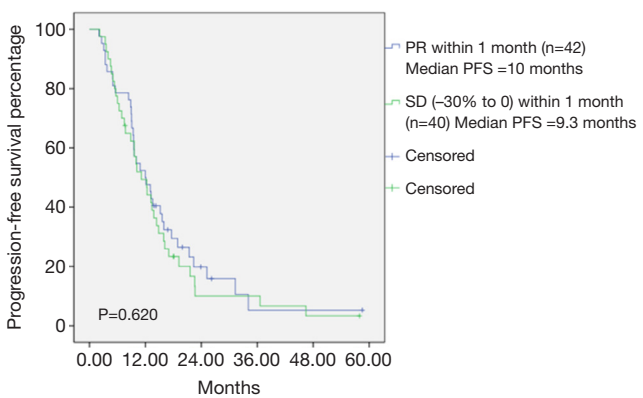


**Figure 2** Kaplan-Meier survival curves for PFS analysis between PR within 1 month and SD (–30% to 0) within 1 month among all patients. PR, partial response; SD, stable disease (tumor shrinkage: –30% to 0); PFS, progression-free survival.

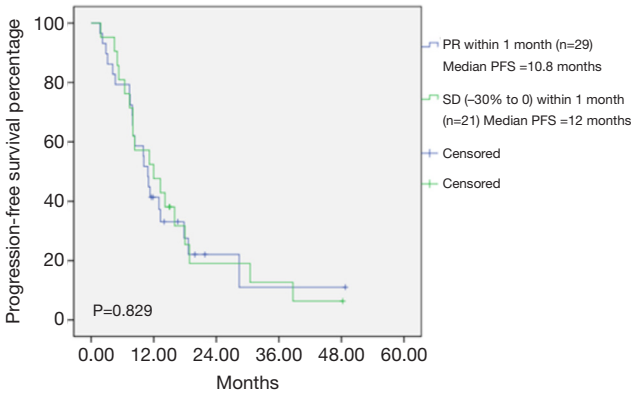


**Figure 3** Kaplan-Meier survival curves for PFS analysis between PR within 1 month and SD (–30% to 0) within 1 month in the *EGFR* 19del mutation group. PR, partial response; SD, stable disease (tumor shrinkage: –30% to 0); PFS, progression-free survival.

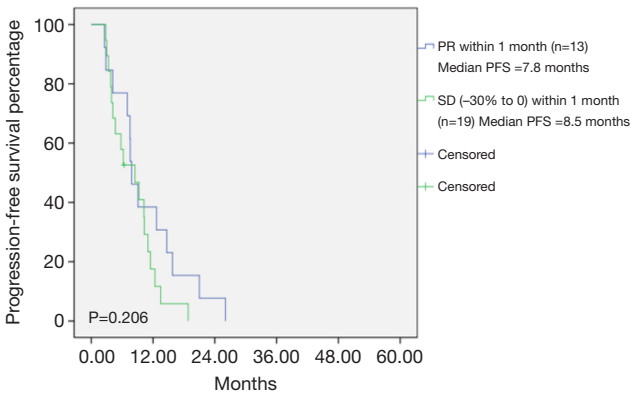


**Figure 4** Kaplan-Meier survival curves for PFS analysis between PR within 1 month and SD (–30% to 0) within 1 month in the *EGFR* 21L858R mutation group. PR, partial response; SD, stable disease (tumor shrinkage: –30% to 0); PFS, progression-free survival.

In the relationship between clinical characteristics and prognosis of total patients, we found that age, *EGFR* mutation type, and T staging had effects on PFS after first-line *EGFR*-TKI treatment. A similar retrospective study showed no significant correlation between age and PFS (17). However, a significant benefit was found among patients aged more than 65 years old in our study. This maybe due to the fact that elderly patients have lower metabolic rates and slower tumor growth than younger patients. For different mutation subtypes, it has been previously reported that *EGFR* 19del mutation has a better prognosis than *EGFR* 21L858R mutation (18), which was confirmed in our study.

According to the IPASS and EURTAC trial (9,10), patients with *EGFR* mutation received gefitinib and erlotinib respectively, compared with chemotherapy, the median PFS was 9.5 and 9.7 months. The ICOGEN trial shows that icotinib is not inferior to gefitinib in improving PFS (11). These findings also support the conclusion that there is no significant difference in PFS among these three drugs.

Regarding metastasis, studies have shown that patients with liver metastasis have a significantly shorter PFS after targeted therapy than those without liver metastasis (19), which may be due to the dual blood supply of the liver. However, we did not find this difference because of the small number of patients with liver metastasis. Similarly, bone metastasis and brain metastasis were not shown to be related to PFS, which may be related to simultaneous receiving of targeted therapy and local treatment.

In conclusion, for patients with *EGFR*-TKI-sensitive advanced NSCLC, there is no correlation between preliminary efficacy (tumor shrinkage within 1 month) and PFS after first-line *EGFR*-TKI treatment. Whether this is related to OS will be reported in the subsequent analysis, because the follow-up data are not yet mature.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study protocol was approved by the Ethics Committee of Shanghai Chest Hospital [KS(Y)1708] and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008).

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