Survival-associated factors of first-line EGFR-tyrosine kinase inhibitor responders and non-responders in lung adenocarcinoma patients with common EGFR mutations

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Abstract. The aim of the present retrospective cohort study was to elucidate the clinical presentation of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) responders and non-responders in lung adenocarcinoma patients with common EGFR mutations. The cohort included 131 lung adenocarcinoma patients with common exon 19 or exon 21 EGFR mutations, who were receiving first-line EGFR-TKI therapy. The patient characteristics, treatment regimen and outcomes were recorded and analyzed. Of the 131 patients, 104 (79.3%) responded to treatment, while 27 (20.7%) did not. A significantly longer median progression-free survival (PFS) [14.3, 95% confidence interval (CI): 12.2-18.4 vs. 5.7, 95% CI: 2.7-9.9 months; P<0.001] and overall survival (OS) (42.2, 95% CI: 28.1-58.1 vs. 11.5, 95% CI: 8.3-19.7 months; P<0.001) were observed in responders compared with non-responders. In responders, bone [hazard ratio (HR)=1.87, 95% CI: 1.11-3.20, P=0.021] and pleural (HR=2.40, 95% CI: 1.37-4.22, P=0.002) metastasis were independent factors of PFS. Exon 19 mutations (HR=0.38, 95% CI: 0.19-0.76, P=0.006), Eastern Cooperative Oncology Group performance status score ≥2 (HR=3.53, 95% CI: 1.42-8.75, P=0.007) and bone metastasis (HR=2.01, 95% CI: 1.05-3.85, P=0.034), were independent factors of OS. In non-responders, smoking (HR=3.97, 95% CI: 1.13-13.91, P=0.031) was an independent factor of PFS. Different survival-associated factors were observed between EGFR-TKI responders and non-responders. The development of new treatment strategies should be advocated in EGFR-TKI non-responders.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, and the majority of the patients are at the advanced stages of the disease at the time of diagnosis (1). Traditional chemotherapy regimens for advanced-stage lung cancer have exhibited modest efficacy in prolonging survival, and are associated with undesirable side effects (2,3). Previously, therapy targeted towards the epidermal growth factor receptor (EGFR) pathway has achieved great success in the treatment of lung cancer. The EGFR pathway is an attractive target for therapy, as EGFR signaling plays an important role in the growth, proliferation and survival of several solid tumors, including non-small-cell lung cancer (NSCLC) (4). A subgroup of patients with NSCLC harbor specific mutations in the tyrosine kinase domain of the EGFR gene, which are correlated with favorable clinical responsiveness to EGFR tyrosine kinase inhibitor (TKI) therapy (5). All mutations appear to be limited to exons 18, 19, 20 and 21 of the EGFR gene (6), and are most frequently observed in lung adenocarcinoma patients (7,8). Missense mutations in exon 21 (L858R) and in-frame deletions in exon 19 are the most frequent EGFR-TKI-sensitive mutations (80%) in NSCLC patients (9). Both the exon 19 deletion and the exon 21 missense mutation are common EGFR mutations that are associated with a favorable response to first-line treatment with gefitinib (10,11), as well as other EGFR-TKIs, including erlotinib (12) and afatinib (13),
compared with standard chemotherapy in NSCLC patients. In NSCLC patients with EGFR mutations, the overall response rate (ORR) to first-line EGFR-TKI therapy is 66.9-83%, with a progression-free survival (PFS) of 9.2-13.1 months (10-13). Despite the favorable response to EGFR-TKIs in NSCLC patients with EGFR mutations, ~20-30% of patients do not respond to EGFR-TKIs, and the clinical phenotypes and survival-associated factors of these EGFR-TKI responders and non-responders have not been previously described.

The aim of the present study was to elucidate the clinical presentation and significance of EGFR-TKI responders and non-responders in lung adenocarcinoma patients with common exon 21 and 19 EGFR activating mutations.

Patients and methods

Patients and study design. The present retrospective cohort study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital. The cohort comprised 131 lung adenocarcinoma patients from the Chang Gung Memorial Hospital, Chiayi Branch (Puzi, Taiwan) (IRB No. 201600601B0), who had been diagnosed between December 2010 and January 2015. All participants were previously treatment-naïve advanced-stage (stage IIIIB or IV) lung adenocarcinoma patients. The EGFR mutation status at exons 18, 19, 20 and 21 of the EGFR gene was determined by Sanger sequencing (8) or by using the Therascreen® EGFR RGQ PCR kit (Qiagen, Manchester, UK) (14). All the patients received first-line EGFR-TKI therapy (gefitinib, erlotinib or afatinib) and had EGFR mutations at exon 19 or 21. Patients with combined exon 18 or 20 mutations were excluded from the study. Follow-up was extended from the first diagnosis of advanced-stage lung cancer to October 2016. The clinical phenotypes of these patients were recorded and analyzed. The response of the lesions was evaluated by chest computed tomography, brain magnetic resonance or bone scan, according to the Response Evaluation Criteria in Solid Tumors 1.1 (15) at 3 months after the initiation of treatment. EGFR-TKI responders were defined as complete responders (CR) or partial responders (PR), while non-responders were defined as those having stable disease (SD) or progressive disease (PD) at 3 months after the initiation of EGFR-TKI therapy. PFS is defined as the time from the first treatment to PD or death. Overall survival (OS) is defined as the time from diagnosis to death from any cause, or until the patients were censored at the last follow-up.

Statistical analysis. The Pearson’s χ² test was used to determine the correlations between the categorical variables in the different groups. Survival analysis was performed using a Kaplan-Meier analysis and log-rank test. Multivariate analysis was performed by Cox proportional-hazards regression, and factors that were determined as significant by the log-rank test were included in the analysis. A P-value of <0.05 was considered as statistically significant. All statistical tests were performed using MedCalc software, version 15 (MedCalc Software, Ostend, Belgium).

Results

Clinical characteristics common to all first-line EGFR-TKI patients. In total, 131 patients were enrolled in the present study (Table I). The median age was 70.0 years. The majority of the patients were female (n=72, 55%), non-smokers (n=115, 87.8%), and had stage IV disease (n=121, 92.4%). Of the 131 patients, 59 (45%) had exon 19 deletions and 72 (55%) had exon 21 missense EGFR mutations. The EGFR-TKIs gefitinib (n=99, 75.6%), erlotinib (n=27, 20.6%) or afatinib (n=5, 3.8%) were used as the first-line therapy in these patients. Three months after EGFR-TKI treatment, the tumor response to treatment was evaluated. PR was observed in 104 (79.3%), SD in 12 (9.2%), and PD in 15 (11.5%) patients. There were no CR patients. The ORR to EGFR-TKIs was 79.3%, and the disease control rate (DCR) was 88.5%. The median PFS for all first-line EGFR-TKI patients was 12.7 months (95% CI: 12.0-16.70 months), and the median OS was 32.7 months (95% CI: 24.7-57.1 months).

Survival of first-line EGFR-TKI responders and non-responders. EGFR-TKI responders and non-responders were identified based on their response to treatment. A total of 104 (79.3%) EGFR-TKI responders (CR + PR) and 27 (20.7%) non-responders (SD + PD) were identified. No significant differences were observed between EGFR-TKI responders and non-responders in terms of sex, smoking history, age, EGFR-TKI use, EGFR mutation status, carcinoembryonic antigen, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and cancer stage (Table I). A significantly higher proportion of brain metastasis was observed in EGFR-TKI responders compared with non-responders (31.7 vs. 7.4%, respectively; P=0.011; Table I). A significantly longer median PFS was observed in EGFR-TKI responders (14.3 months, 95% CI: 12.2-18.4 months) compared with that in non-responders (5.7 months, 95% CI: 2.7-9.9 months; P=0.001; Fig. 1A). We also observed a significantly longer median OS in responders (42.2 months, 95% CI: 28.1-58.1 months) compared with that in non-responders (11.5 months, 95% CI: 8.3-19.7 months; P=0.001; Fig. 1B).

Characteristics of survival in patients treated with first-line EGFR-TKIs. The associations between measured clinical variables and survival were evaluated. According to the univariate analysis, EGFR-TKI responder status (HR=0.33, 95% CI: 0.16-0.68, P<0.001) and old age (>65 years) (HR=0.64, 95% CI: 0.41-1.00, P=0.038) were significantly associated with a favorable PFS (Table II). Conversely, male sex (HR=1.66, 95% CI: 1.07-2.58, P=0.018), bone metastasis (HR=1.66, 95% CI: 1.07-2.58, P=0.024) and pleural metastasis (HR=1.62, 95% CI: 1.00-2.77, P=0.022) were significantly associated with an unfavorable PFS (Table II). According to the multivariate analysis, EGFR-TKI responder status (HR=0.25, 95% CI: 0.15-0.42, P=0.001), old age (HR=0.58, 95% CI: 0.36-0.92, P=0.020) and male sex (HR=1.70, 95% CI: 1.07-2.67, P=0.024) remained independent factors for PFS (Table II). According to the univariate analysis, exon 19 mutations (HR=0.55, 95% CI: 0.33-0.92, P=0.027) and EGFR-TKI responder status (HR=0.30, 95% CI: 0.14-0.67, P=0.001) were significantly associated with a favorable OS (Table III). By contrast, ECOG PS ≥2 (HR=2.21, 95% CI: 0.79-6.18, P=0.031) and bone metastasis (HR=1.79, 95% CI: 1.04-3.10, P=0.020) were significantly associated with an unfavorable OS (Table III). According to the multivariate analysis, EGFR-TKI responder status (HR=0.30, 95% CI: 0.17-0.54, P<0.001),
Table I. Clinical characteristics of patients treated with first-line EGFR-TKIs.

|                        | Total | Responders | Non-responders | P-value |
|------------------------|-------|------------|----------------|---------|
| Patients               | 131   | 104        | 27             |         |
| Sex                    |       |            |                | 0.426   |
| Male                   | 59 (45.0) | 45 (43.2) | 14 (51.9)      |         |
| Female                 | 72 (55.0) | 59 (56.8) | 13 (48.1)      |         |
| Smoking                |       |            |                | 0.645   |
| Yes                    | 16 (12.2) | 12 (11.5) | 4 (14.8)       |         |
| No                     | 115 (87.8) | 92 (88.5) | 23 (85.2)      |         |
| Age (years)            |       |            |                | 0.219   |
| ≥65                    | 82 (62.6) | 61 (58.6) | 21 (77.8)      |         |
| <65                    | 49 (37.4) | 43 (41.4) | 6 (22.2)       |         |
| TKI                    |       |            |                | 0.157   |
| Erlotinib              | 27 (20.6) | 24 (23.0) | 3 (11.1)       | 0.059   |
| Gefitinib              | 99 (75.6) | 75 (72.1) | 24 (88.9)      |         |
| Afatinib               | 5 (3.8) | 5 (4.8)    |               |         |
| Mutations              |       |            |                | 0.350   |
| Exon 19                | 59 (45.0) | 49 (47.1) | 10 (37.0)      |         |
| Exon 21                | 72 (55.0) | 55 (52.9) | 17 (63.0)      |         |
| Stage                  |       |            |                | 0.961   |
| IIIb                   | 10 (7.6) | 8 (7.7) | 2 (7.4)       |         |
| IV                     | 121 (92.4) | 96 (92.3) | 25 (92.6)      |         |
| CEA (ng/ml)            | 95 | 79 | 156 | 0.325 |
| ECOG PS                |       |            |                | 0.724   |
| ≤1                     | 119 (90.8) | 94 (90.4) | 25 (92.6)      |         |
| ≥2                     | 12 (9.2) | 10 (9.6) | 2 (7.4)       |         |
| Metastatic sites       |       |            |                |         |
| Lung                   | 42 (32.1) | 36 (34.6) | 6 (22.2)      | 0.221   |
| Brain                  | 35 (26.7) | 33 (31.7) | 2 (7.4)       | 0.011*  |
| Liver                  | 15 (11.4) | 12 (11.5) | 3 (11.1)      | 0.951   |
| Bone                   | 51 (38.9) | 37 (35.6) | 14 (51.9)      | 0.124   |
| Adrenal                | 9 (6.9) | 8 (7.7) | 1 (3.7) | 0.467 |

*P<0.05. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

Figure 1. (A) PFS and (B) OS of EGFR-TKI responders and non-responders in first-line EGFR-TKI lung adenocarcinoma patients with common EGFR mutations. PFS, progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
Survival-associated factors in first-line EGFR-TKI responders and non-responders. Since the initial response to EGFR-TKI treatment was significantly associated with PFS and OS according to both univariate and multivariate analysis, the characteristics of EGFR-TKI responders and non-responders were then analyzed separately.

According to the univariate analysis for EGFR-TKI responders, old age (HR=0.56, 95% CI: 0.34-0.93, P=0.018) was significantly associated with a favorable PFS, while ECOG PS ≥2 (HR=1.62, 95% CI: 1.02-2.56, P=0.024) remained an independent factor for OS (Table III).
pleural metastasis (HR=2.01, 95% CI: 1.08-3.73, P=0.006) was significantly associated with an unfavorable PFS (Table IV). According to the multivariate analysis, bone metastasis (HR=1.87, 95% CI: 1.11-3.20, P=0.021) and pleural metastasis (HR=2.40, 95% CI: 1.37-4.22, P=0.002) were independent factors for PFS (Table IV).

Exon 19 mutations (HR=0.40, 95% CI: 0.22-0.74, P=0.006) were significantly associated with a favorable OS, while ECOG PS ≥2 (HR=2.61, 95% CI: 0.73-9.30, P=0.023) and bone metastasis (HR=1.92, 95% CI: 0.98-3.77, P=0.030) were significantly associated with an unfavorable OS (Table V). Exon 19 mutations (HR=0.38, 95% CI: 0.19-0.76, P=0.006), ECOG PS ≥2 (HR=3.53, 95% CI: 1.42-8.75, P=0.007) and bone metastasis (HR=2.01, 95% CI: 1.05-3.85, P=0.034) remained independent factors of OS according to the multivariate analysis (Table V).

Factors associated with EGFR-TKI non-responders were also analyzed. According to the univariate analysis, male

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Table IV. Clinical variables associated with PFS in first-line EGFR-TKI responders.

| Covariates            | Univariate analysis |                  |          |                  |                  |
|-----------------------|---------------------|------------------|----------|------------------|------------------|
|                       | P-value             | HR               | 95% CI   | P-value          | HR               | 95% CI           |
| Male sex              | 0.150               | 1.42             | 0.86-2.36|                  |                  |                  |
| Exon 19 mutation      | 0.189               | 0.72             | 0.44-1.19|                  |                  |                  |
| Smoking               | 0.614               | 1.21             | 0.54-2.68|                  |                  |                  |
| Old age (≥65 years)   | 0.018               | 0.56             | 0.34-0.93|                  |                  |                  |
| ECOG PS ≥2            | 0.657               | 1.23             | 0.45-3.33|                  |                  |                  |
| Gefitinib             | 0.474               | 1.24             | 0.71-2.21|                  |                  |                  |
| Metastasis            |                     |                  |          |                  |                  |                  |
| Lung                  | 0.395               | 1.25             | 0.73-2.13|                  |                  |                  |
| Brain                 | 0.524               | 0.84             | 0.49-1.43|                  |                  |                  |
| Liver                 | 0.081               | 1.80             | 0.78-4.18|                  |                  |                  |
| Bone                  | 0.063               | 1.58             | 0.92-2.72| 0.021b           | 1.87             | 1.11-3.20        |
| Adrenals              | 0.512               | 1.32             | 0.51-3.39|                  |                  |                  |
| Pleura                | 0.006b              | 2.01             | 1.08-3.73| 0.002b           | 2.40             | 1.37-4.22        |

aReference group is exon 21. bP<0.05. PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

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Table V. Clinical variables associated with OS in first-line EGFR-TKI responders.

| Covariates            | Univariate analysis |                  |          |                  |                  |
|-----------------------|---------------------|------------------|----------|------------------|------------------|
|                       | P-value             | HR               | 95% CI   | P-value          | HR               | 95% CI           |
| Male sex              | 0.456               | 1.26             | 0.67-2.39|                  |                  |                  |
| Exon 19 mutation      | 0.006b              | 0.40             | 0.22-0.74| 0.006b           | 0.38             | 0.19-0.76        |
| Smoking               | 0.897               | 0.93             | 0.34-2.55|                  |                  |                  |
| Old age (≥65 years)   | 0.844               | 1.06             | 0.57-1.99|                  |                  |                  |
| ECOG PS ≥2            | 0.023b              | 2.61             | 0.73-9.30| 0.007b           | 3.53             | 1.42-8.75        |
| Gefitinib             | 0.158               | 1.83             | 0.89-3.76|                  |                  |                  |
| Metastasis            |                     |                  |          |                  |                  |                  |
| Lung                  | 0.206               | 1.49             | 0.76-2.90|                  |                  |                  |
| Brain                 | 0.376               | 1.33             | 0.67-2.64|                  |                  |                  |
| Liver                 | 0.081               | 2.11             | 0.66-6.72|                  |                  |                  |
| Bone                  | 0.030b              | 1.92             | 0.98-3.77| 0.034b           | 2.01             | 1.05-3.85        |
| Adrenals              | 0.235               | 0.32             | 0.10-1.05|                  |                  |                  |
| Pleura                | 0.875               | 1.06             | 0.53-2.08|                  |                  |                  |

aReference group is exon 21. bP<0.05. OS, overall survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.
sex (HR=2.24, 95% CI: 0.91-5.47, P=0.045) and smoking (HR=3.24, 95% CI: 0.59-17.70, P=0.020) were significantly associated with an unfavorable PFS, and smoking (HR=3.97, 95% CI: 1.13-13.91, P=0.031) remained an independent factor of PFS according to the multivariate analysis (Table VI). No factor analyzed in the present study was associated with OS in EGFR-TKI non-responders (data not shown).

**Discussion**

In the present study, 20.3% of lung adenocarcinoma patients with common sensitizing exon 21 and exon 19 EGFR mutations were EGFR-TKI non-responders. Our results are similar to those of previous studies on first-line TKI treatment, in which EGFR-TKI non-responders accounted for 20-30% of the study group (10-13). In the present study, EGFR-TKI non-responders had a poor prognosis. The clinical factors associated with PFS and OS were also assessed and it was observed that, in EGFR-TKI responders, bone and pleural metastasis were independent factors for unfavorable PFS. Poor ECOG PS (≥2) and bone metastasis were independent factors for unfavorable OS, and exon 19 deletions were an independent factor for favorable OS. In EGFR-TKI non-responders, smoking was an independent factor for unfavorable PFS.

PFS and OS were reduced in EGFR-TKI non-responders, confirming the results of an earlier study, in which the median OS was 21 months (95% CI: 26.1-30.4) in responders compared with 8 months (95% CI: 8.7-15.8) in non-responders (16). Based on the multivariate analysis, EGFR-TKI non-responding status was found to be a strongly unfavorable factor for both PFS and OS in patients receiving first-line EGFR-TKI therapy. Rapid progression of lung cancer after the initiation of EGFR-TKI therapy has been reported to be a poor prognostic factor for survival outcomes (17). Our results further suggest that EGFR-TKI non-responders are distinctly different from EGFR-TKI responders. Since this group of patients had a worse prognosis, a treatment strategy that overcomes primary resistance to EGFR-TKI is urgently needed. Close monitoring of EGFR-TKI treatment response is also mandatory for early detection of EGFR-TKI non-responders, so that treatment may be adjusted accordingly.

Exon 19 deletions have been associated with better outcomes compared with L858R mutations in EGFR-TKI patients as, reported in several studies (18-20). In the present study, exon 19 deletions were found to be an independent predictor of outcome in first-line EGFR-TKI responders. Exon 19 deletions have been previously associated with better survival rates compared with exon 21 mutations in gefitinib-treated NSCLC patients, due to the differential inhibition of downstream signaling (21). Recently, exon 19 deletions were reported to be associated with a better outcome after afatinib therapy, compared with that of the exon 21 L858R mutation. Altogether, exon 19 deletions and L858R mutations characterize two distinct groups of patients and, therefore, different clinical treatment strategies for these patients should be considered in the future. A reduced frequency of exon 19 deletions has also recently been reported in EGFR-TKI non-responders (16). However, no significant differences in the frequency of exon 19 deletions and L858R mutations were observed, which may be due to the limited number of patients in this cohort.

In the present study, poor baseline ECOG PS (≥2) was associated with an unfavorable OS in EGFR-TKI responders, which is similar to previously reported results (17). However, we did not observe a significant effect of poor ECOG PS on PFS, which may indicate that EGFR-TKIs are effective and well-tolerated in responders. In addition, 35.6% of EGFR-TKI responders had developed bone metastasis at the time of diagnosis of lung cancer, and the overall incidence of bone

| Covariates                  | Univariate analysis | Multivariate analysis |
|-----------------------------|---------------------|-----------------------|
|                             | P-value | HR | 95% CI | P-value | HR | 95% CI |
| Male sex                   | 0.045a  | 2.24 | 0.91-5.47 |          |      |       |
| Exon 19 mutation           | 0.610   | 0.79 | 0.31-1.97 | 0.031a  | 3.97 | 1.13-13.91 |
| Smoking                    | 0.020a  | 3.24 | 0.59-17.70 |          |      |       |
| Old age (≥65 years)        | 0.053   | 0.41 | 0.12-1.40 |          |      |       |
| ECOG PS ≥2                 | 0.277   | 2.17 | 0.28-16.56 |          |      |       |
| Gefitinib                  | 0.455   | 1.56 | 0.54-4.54 |          |      |       |
| Metastasis                 |          |     |        |          |      |       |
| Lung                       | 0.717   | 1.20 | 0.41-3.47 |          |      |       |
| Brain                      | 0.642   | 0.72 | 0.20-2.62 |          |      |       |
| Liver                      | 0.718   | 1.25 | 0.33-4.72 |          |      |       |
| Bone                       | 0.951   | 1.03 | 0.43-2.48 |          |      |       |
| Adrenal                    | 0.077   | 4.92 | 0.07-356.78 |          |      |       |
| Pleura                     | 0.552   | 0.77 | 0.32-1.87 |          |      |       |

aP<0.05. Reference group is exon 21. PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.
metastasis in patients with EGFR mutations was not higher compared with that reported previously (22). Bone metastasis was found to be associated with unfavorable PFS and OS. EGFR-TKIs prolong survival in patients with EGFR mutations and bone metastasis (23). However, our results highlight that management of bone metastasis should be a priority in EGFR-TKI responders.

Smoking at the time of diagnosis of lung cancer was associated with unfavorable PFS in EGFR-TKI non-responders. Indeed, smoking for ≥30 pack-years is associated with a decreased ORR and DCR in lung adenocarcinoma with activation EGFR mutations (24). No clinical variables were associated with OS in EGFR-TKI non-responders, which may be attributed to the relatively short survival and small number of these patients. In addition, non-response to EGFR-TKIs (primary resistance) may be associated with underlying genetics or molecular mechanisms in lung cancer cells. Several mechanisms for primary EGFR-TKI resistance have been proposed, including v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog mutations (25), phosphoinositide-3-kinase catalytic subunit α mutation (26), de novo MET amplification (27,28), Bim deletion polymorphisms (29,30), and phosphatase and tensin homolog loss (31).

De novo T790M mutations of the EGFR gene have also been reported to be associated with poorer response to first-line EGFR-TKI treatment (32). Since patients with de novo T790M mutations were excluded from the present study, we hypothesized that other genetic or molecular changes may be implicated in EGFR-TKI resistance in EGFR-TKI non-responders in the present study, and these changes warrant further investigation. Although this study was limited by the small cohort size and limited number of EGFR mutations, the results may help elucidate the clinical presentation of the EGFR-TKI response, and contribute to the development of novel treatment strategies for lung adenocarcinoma patients with common EGFR mutations.

In summary, it was demonstrated that different prognosis and survival-associated factors are observed in EGFR-TKI responders and non-responders. These groups of patients should therefore be considered as two distinct groups, and novel treatment strategies should be developed and applied to EGFR-TKI non-responders.

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Competing interests

The authors declare that they have no competing interests.

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