Subsequent treatment of epidermal growth factor receptor-tyrosine kinase inhibitor failure in patients with advanced lung adenocarcinoma

Xiaojuan Qiao1,2, Ye Zhang3, Jinghui Wang4, Jingying Nong4, Xi Li4, Xinjie Yang4, Jialin Lv4, Hui Zhang4, Na Qin4, Quan Zhang4, Wentao Yue1 & Shucai Zhang4

1 Department of Cellular and Molecular Biology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China
2 Health Care Ward, The First Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China
3 Department of Pharmacology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China
4 Department of Medical Oncology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China

Keywords
Epidermal growth factor receptor; failure; lung adenocarcinoma; tyrosine kinase inhibitor.

Abstract
Background: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) effectively treat advanced non-small cell lung cancer with EGFR-mutation. However, most patients develop acquired resistance without effective therapy subsequent to EGFR-TKI failure. We evaluated the efficacy of subsequent treatment strategies for EGFR-TKI resistance.

Methods: We retrospectively analyzed 240 patients with advanced lung adenocarcinoma with EGFR-TKI failure and following subsequent treatment. According to the first subsequent strategies after EGFR-TKI failure, patients were divided into groups of EGFR-TKI continuation (21 cases), EGFR-TKI continuation with chemotherapy (23 cases), chemotherapy alone (143 cases), and best supportive care (BSC) (53 cases).

Results: Except for 53 cases of BSC, the disease control rates (DCR) of the remaining 187 patients in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were 66.7%, 73.9%, and 44.8%, respectively. The median post-progression progression-free survival (PFS) for the three groups was 3.0, 3.3, and 2.0 months, respectively. The DCR for the EGFR-TKI continuation with chemotherapy group was significantly higher than the chemotherapy alone group (P = 0.006). The post-progression PFS of the EGFR-TKI continuation with chemotherapy group was significantly longer than the chemotherapy alone group (P = 0.037). The median overall survival in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups were 6.9, 11.6, 8.8, and 0.9 months, respectively. Compared to the BSC group, all groups achieved a survival benefit (P < 0.001).

Conclusions: EGFR-TKI continuation with chemotherapy could provide benefits for patients with acquired resistance to EGFR-TKI.

Introduction
Non-small cell lung cancer (NSCLC) is the main type of lung cancer, accounting for 85% of all lung cancers. Because of the lack of early symptoms and specific clinical manifestations, early diagnosis is very difficult and about 70% of NSCLC patients are diagnosed in advanced stage. Chemotherapy for advanced NSCLC has entered the plateau stage.1 Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), represented by gefitinib, erlotinib, and icotinib, have changed the treatment model of advanced NSCLC, in which EGFR mutation is the most effective predictor of EGFR-TKI
efficacy. Many large clinical studies, such as IPASS, WJTOG3405, NEJ002, OPTIMAL, and EURTAC show that EGFR-TKI efficacy in advanced NSCLC with EGFR mutations can reach 60–80%, and progression-free survival (PFS) can be longer than a year.2–6 However, most patients will inevitably develop EGFR-TKI failure as a result of resistance against EGFR-TKIs. Small sample and single-center studies have found that EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone will benefit some patients.7–12 This study aimed to conduct a retrospective analysis to further explore the effects of subsequent treatment after EGFR-TKI failure on efficacy and survival in patients with advanced lung adenocarcinoma.

Materials and methods

General information
This retrospective study included 240 patients who had received EGFR-TKIs at the Beijing Chest Hospital for ≥3 months, demonstrated failure, and received subsequent treatment from 6 November 2005 to 20 November 2013. All patients were histologically or cytologically diagnosed with lung adenocarcinoma, and they had reached clinical stage IV after EGFR-TKI failure.13

Treatment methods
During initial EGFR-TKI treatment, 104 patients received gefitinib, 84 received erlotinib, and 52 received icotinib with conventional EGFR-TKI doses, including 250 mg of gefitinib once daily, 150 mg of erlotinib once daily, and 125 mg of icotinib three times daily. The first subsequent treatment after EGFR-TKI failure consisted of the following: EGFR-TKI continuation (continuing the same EGFR-TKI agent), EGFR-TKI continuation with chemotherapy, chemotherapy alone, and best supportive care (BSC). We evaluated tumor response in patients who received EGFR-TKI every four weeks based on computed tomography scans, then performed additional assessments every eight weeks. For patients who received chemotherapy, we performed assessments every two cycles. In patients whose symptoms deteriorated over the course of chemotherapy, imaging review was conducted to re-evaluate efficacy.

Efficacy assessment
We applied Response Evaluation Criteria in Solid Tumors (1.1) to assess efficacy, which was divided into: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).14 The evaluation index included: disease control rate (DCR), PFS, and overall survival (OS). The initial EGFR-TKI treatment PFS was defined as the time from the start of EGFR-TKI treatment to PD identification. Post-progression PFS was defined as the time from confirmed PD to the second progression or death. OS was defined as the time from confirmed PD of initial EGFR-TKI failure to death. The survey was conducted using outpatient and telephone follow-up. Follow-up concluded on 30 April 2014, after which data was censored for surviving patients.

Statistical analysis
We performed statistical analysis using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). We analyzed differences in efficacy using the Chi-square test and a logistic regression model including clinically relevant confounders. We used the Kaplan–Meier method to estimate survival curves, the log-rank test to compare survival curves among different groups, and the multivariate Cox proportional hazards regression model to evaluate independent prognostic factors associated with PFS and OS. As multivariate analysis, all clinical factors were included in the model. All statistical tests were two-sided and values of $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics
During initial EGFR-TKI treatment, the proportions of patients at the first, second, third, fourth, and fifth lines were 32.9%, 43.3%, 21.7%, 1.7%, and 0.4%, respectively. The rate of EGFR mutation testing was 38.75%. The objective response rate (ORR) of initial EGFR-TKI treatment was 30%, and the median PFS was 5.1 months. At initial EGFR-TKI failure, the patients’ median age was 57 years (ranging from 26 to 91 years). Women accounted for 49.6% (119/240), nonsmokers 58.3% (140/240), and the Eastern Cooperative Oncology Group performance status (PS) 0–1 was 63.3% (152/240). According to the first subsequent treatment after EGFR-TKI failure, patients were divided into four groups: EGFR-TKI continuation (21 cases), EGFR-TKI continuation with chemotherapy (23 cases), chemotherapy alone (143 cases), and BSC groups (53 cases). All 240 patients were evaluable for OS. With the exception of the 53 patients in the BSC group, 187 patients in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were evaluated for post-progression efficacy and PFS.

The median age of patients at initial EGFR-TKI failure in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups were 60, 59, 55, and 58 years, respectively. There were more patients of PS 0–1 at initial EGFR-TKI failure who received EGFR-TKI continuation with chemotherapy (82.6%) and chemotherapy

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alone (83.2%) compared with patients of PS 2 at initial EGFR-TKI failure who received EGFR-TKI continuation (57.1%) and BSC (90.6%). Four patients (19%) had activating EGFR mutations in the EGFR-TKI continuation group, nine (39.1%) in the EGFR-TKI continuation with chemotherapy, 45 (31.5%) in the chemotherapy alone, and five patients (9.4%) in the BSC group. The majority of patients in the four groups accepted initial EGFR-TKI as a second-line and above therapy. The characteristics of the four groups are listed in Table 1.

### Table 1 Clinical characteristics of enrolled patients

| Characteristics of TKI failure | TKI n (%) | TKI plus Chemo n (%) | Chemo n (%) | BSC n (%) |
|-------------------------------|-----------|-----------------------|-------------|-----------|
| Total                         | 21        | 23                    | 143         | 53        |
| Characteristics of TKI failure |           |                       |             |           |
| Age of TKI failure (years)    |           |                       |             |           |
| Median (range)                | 60 (30–85)| 59 (45–75)            | 55 (26–81)  | 58 (35–91)|
| ≤65                           | 15 (71.4) | 17 (73.1)             | 114 (79.7) | 38 (71.7)|
| >65                           | 6 (28.6)  | 6 (26.9)              | 29 (20.3)  | 15 (28.3)|
| Gender                        |           |                       |             |           |
| Male                          | 11 (52.4)| 15 (65.2)             | 62 (43.4)  | 33 (62.3)|
| Female                        | 10 (47.6)| 8 (34.8)              | 81 (56.6)  | 20 (37.7)|
| Smoking status                |           |                       |             |           |
| Never                         | 11 (52.4)| 10 (43.5)             | 94 (65.7)  | 25 (47.2)|
| Smoker                        | 10 (47.6)| 13 (56.5)             | 49 (34.3)  | 28 (52.8)|
| ECOG PS of TKI failure        |           |                       |             |           |
| 0–1                           | 9 (42.9) | 19 (82.6)             | 119 (83.2) | 5 (9.4)  |
| ≥2                            | 12 (57.1)| 4 (17.4)              | 24 (16.8)  | 48 (90.6)|
| Characteristics of initial TKI |           |                       |             |           |
| EGFR mutation                 |           |                       |             |           |
| Activating mutation           | 4 (19.0) | 9 (39.1)              | 45 (31.5)  | 5 (9.4)  |
| Wild type                     | 2 (9.5)  | 2 (8.7)               | 14 (9.8)   | 12 (22.6)|
| Unknown                       | 15 (71.4)| 12 (52.2)             | 84 (58.7)  | 36 (67.9)|
| Line of initial TKI           |           |                       |             |           |
| 1st                           | 8 (38.1) | 4 (17.4)              | 48 (33.6)  | 19 (35.8)|
| ≥2nd                          | 13 (61.9)| 19 (82.6)             | 95 (66.4)  | 34 (64.2)|
| Best response to initial TKI  |           |                       |             |           |
| PR                            | 6 (28.6) | 6 (26.1)              | 54 (37.8)  | 6 (11.3) |
| SD                            | 15 (71.4)| 17 (73.9)             | 89 (62.2)  | 47 (88.7)|
| PFS of initial TKI            |           |                       |             |           |
| ≤6 months                     | 13 (61.9)| 7 (30.4)              | 74 (51.7)  | 42 (79.2)|
| >6 months                     | 8 (38.1) | 16 (69.6)             | 69 (48.3)  | 11 (20.8)|

BSC, best supportive care; chemo, chemotherapy; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI plus chemo, EGFR-TKI continuation with chemotherapy; TKI, tyrosine kinase inhibitors.

### Efficacy of different therapeutic strategies after epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) failure

Among 187 patients, there was no complete response, seven PR (3.7%), 88 SD (47.1%), and 92 PD cases (49.2%). The ORR was 3.7%. The ORR of the EGFR-TKI continuation group was 14.3% and the chemotherapy alone group 2.8%. There were no PR patients in the EGFR-TKI continuation with chemotherapy group. Because cases of PR were rare, we performed no further statistical analysis. The overall DCR was 50.8%, and the rates in the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were 66.7%, 73.9%, and 44.8%, respectively. The difference among these three groups was significant ($P = 0.01$) (Table 2). The DCR of the EGFR-TKI continuation with chemotherapy group was significantly higher than the chemotherapy alone group (odds ratio [OR] = 1.651, 95% confidence interval [CI] = 1.219–2.237, $P = 0.009$). The DCR difference between the EGFR-TKI continuation and EGFR-TKI continuation with chemotherapy groups, and that between the EGFR-TKI continuation and chemotherapy alone groups, was not significant ($P = 0.559$; $P = 0.06$). Results after balancing confounding factors showed that the DCR of the EGFR-TKI continuation with chemotherapy group was significantly higher than the che-
motherapy alone group (OR = 4.057, 95% CI = 1.485–11.083, P = 0.006). Logistic multivariate analysis indicated that initial EGFR-TKI as a first-line therapy (OR = 2.146, 95% CI = 1.123–4.102, P = 0.021) was an independent predictor of improved efficacy.

Progression-free survival of different treatment strategies after EGFR-TKI failure

The median PFS of 187 patients who received treatment after EGFR-TKI failure was 2.2 months, and six patients were without progression at the last follow-up. The post-progression median PFS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups was 3.0 (95% CI: 1.4–4.6 months), 3.3 (95% CI: 1.6–5.0 months), and 2.0 months (95% CI: 1.6–2.4 months), respectively, and the difference among these three groups was not significant (P = 0.203) (Fig 1a, Table 3). The Cox proportional hazards regression model indicated that the post-progression PFS of the EGFR-TKI continuation with chemotherapy group was significantly longer than that of the chemotherapy alone group (hazard ratio [HR] = 0.611, 95% CI = 0.385–0.971, P = 0.037) (Table 4). The Cox proportional hazards regression model also showed that initial EGFR-TKI treatment as a first-line therapy (HR = 0.705, 95% CI = 0.508–0.978, P = 0.036) and PS 0–1 at initial EGFR-TKI failure (HR = 0.469, 95% CI = 0.319–0.689, P < 0.001), were independent prognostic factors reducing the risk of disease progression.

Overall survival of different treatment strategies after EGFR-TKI failure

The median OS of the 240 patients was 6.5 months. Twenty-four of those patients survived until the final follow-up and 16 patients were lost to follow-up, resulting in a loss to follow-up rate of 6.7%. The median OS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, chemotherapy alone, and BSC groups was 6.9 (95% CI: 2.9–10.9 months), 11.6 (95% CI: 4.0–19.2 months), 8.8 (95% CI: 6.7–10.9 months), and 0.9 months (95% CI: 0.6–1.2 months), respectively, and the difference among these groups was significant (P < 0.001) (Fig 1b, Table 3). Compared with the BSC group, the OS of the EGFR-TKI continuation (P < 0.001), EGFR-TKI continuation with chemotherapy (P < 0.001), and chemotherapy alone groups (P < 0.001) were significantly prolonged. The OS of the EGFR-TKI

Table 2 Efficacy of different treatment strategies after EGFR-TKI failure

| Group | TKI | TKI plus Chemo | Chemo | P   |
|-------|-----|---------------|-------|-----|
| PR    | 3   | 0             | 4     |     |
| SD    | 11  | 17            | 60    |     |
| PD    | 7   | 6             | 79    |     |
| DCR   | 66.7% | 73.9%     | 44.8% | 0.01†|

†Comparison among the three groups. DCR, disease control rate; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; TKI plus chemo, EGFR-TKI continuation with chemotherapy.

Figure 1 Progression-free survival (PFS) and overall survival (OS) curves after epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) progression. (a) PFS curve: TKI versus TKI plus chemo versus chemo; (b) OS curve: TKI versus TKI plus chemo versus chemo versus best supportive care. TKI; TKI plus; Chemo; TKI-censoring; TKI plus-censoring; Chemo-censoring.
Table 3 Univariate analysis of progression-free survival and overall survival after EGFR-TKI failure

| Group                                      | PFS (month) | OS (month) |
|--------------------------------------------|-------------|------------|
| EGFR mutation                              |             |            |
| Activating mutation                        | 2.6         | 10.6       |
| Wild type                                  | 1.6         | 4.6        |
| Unknown                                    | 2.1         | 5.1        |
| Line of initial TKI                        |             |            |
| 1st                                        | 2.8         | 6.1        |
| ≥2nd                                       | 2.0         | 6.9        |
| Best response to initial TKI               |             |            |
| PR                                         | 2.8         | 10.6       |
| SD                                         | 2.1         | 7.3        |
| PFS of initial TKI                         |             |            |
| ≤6 months                                  | 2.1         | 3.8        |
| >6 months                                  | 2.2         | 8.8        |
| Characteristics of TKI failure             |             |            |
| Age of TKI failure (years)                 | 2.2         | 7.2        |
| Gender                                     | 2.0         | 3.5        |
| Smoking status                             |             |            |
| Never                                      | 2.0         | 7.3        |
| Smoker                                     | 2.2         | 4.6        |
| ECOG PS of TKI failure                     |             |            |
| 0–1                                        | 2.5         | 10.9       |
| ≥2                                         | 1.7         | 1.7        |
| Subsequent treatment                       |             |            |
| TKI                                        | 3.0         | 6.9        |
| TKI plus                                   | 3.3         | 11.6       |
| Chemo                                      | 2.0         | 8.8        |
| BSC                                        | –           | 0.9        |

Discussion

Subsequent treatment after EGFR-TKI failure has attracted much attention from researchers. Current studies have shown that among patients with acquired resistance against EGFR-TKI, 50–60% of cases were a result of a second T790M mutation, 15 5–22% were a result of mesenchymal-epithelial transition (MET) gene amplification, 16 and others were caused by factors such as excessive hepatocyte growth factor expression, 17 Gas6-Axl activation, 18 phosphatase and tensin homolog gene expression loss in the downstream pathway, 19 phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha mutation, 20 small-cell lung cancer transformation, 21 and epithelial-to-mesenchymal transition. 22 For patients resistant to EGFR-TKI, the most ideal treatment is to conduct a subsequent biopsy to clarify the resistance mechanism in order to select a targeted therapeutic strategy.
However, in clinical practice, collecting subsequent specimens after EGFR-TKI failure is not possible, and drugs based on the EGFR-TKI resistance mechanism are still in various clinical trial stages. At the 2014 American Society of Clinical Oncology conference, the results of a phase I study of AZD9291 and Lux-lung-5 were reported. However, only a handful of research centers are able to participate in clinical research for new drugs after the first generation of EGFR-TKI resistance. Only a small percentage of patients are suitable for and receive new drug treatment, while most patients resistant to EGFR-TKI have no optional new drug. Therefore, clinical treatment after EGFR-TKI failure mainly adopts existing treatment methods, such as EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone. This study retrospectively analyzed EGFR-TKI failure cases and investigated the effects of subsequent therapeutic strategies on efficacy and patient survival. Our results showed that after EGFR-TKI failure, the EGFR-TKI continuation with chemotherapy group achieved the highest DCR, and the median PFS and median OS were the longest, indicating that EGFR-TKI continuation with chemotherapy might provide benefits for a small percentage of patients.

Pre-clinical studies suggest that EGFR-TKI combined with chemotherapy has synergistic effects on EGFR-TKI acquiring resistant cells. Yoshimura et al. reported a phase II study, the results of which showed that 27 NSCLC patients with stage III-IV EGFR mutations who received EGFR-TKI continuation with pemetrexed after EGFR-TKI failure obtained a favorable response. Shukuya et al. retrospectively analyzed 16 NSCLC patients with gefitinib failure who had obtained CR or PR during gefitinib therapy, and they then received subsequent gefitinib treatment plus paclitaxel. The results demonstrated an ORR of 13%, DCR 75%, median PFS 4.3 months, and median OS of 8.1 months. Our study showed that the EGFR-TKI continuation with chemotherapy group received the most significant clinical benefits among 187 patients with advanced NSCLC who developed EGFR-TKI failure and received subsequent treatment. Our data demonstrated a DCR of 73.9%, and median PFS and OS values of 3.3 and 11.6 months, respectively. However, in our study, the DCR and median PFS of the EGFR-TKI continuation with chemotherapy group were lower than in previous reports, and there were no PR patients. Meanwhile, the median PFS of the EGFR-TKI continuation and chemotherapy alone groups were also lower than in previous retrospective reports, which may be related to the enrolled population. Most patients from previous studies were a selective population, while in this study, patients with sensitive EGFR mutations accounted for 31%; the efficacy of initial EGFR-TKI evaluated as PR accounted for 30%, and without CR; and post-progression treatment as a third-line or above therapy accounted for 66.8%. The difference in OS may be a result of different OS definitions.

Our data showed that the DCR and median PFS and OS of the EGFR-TKI continuation with chemotherapy group were higher than those of the chemotherapy alone group, and the differences in DCR and median PFS were statistically significant. This was similar to another retrospective study, but inconsistent with the preliminary findings of IMPRESS, a phase III randomized study. Goldberg et al. conducted a retrospective study on 78 patients resistant to EGFR-TKIs in a single center, and the results revealed that the efficiency and PFS of the EGFR-TKI continuation with chemotherapy group were both superior to those of chemotherapy alone.

| Variable                      | PFS HR | 95% CI       | P  | OS HR | 95% CI       | P  |
|-------------------------------|--------|--------------|----|-------|--------------|----|
| Line of initial TKI           |        |              |    |       |              |    |
| 1st                           | 0.705  | 0.508–0.978  | 0.036 |       |              |    |
| ≥2nd                          |        |              |    |       |              |    |
| Age of TKI failure (years)    |        |              |    |       |              |    |
| ≤65                           | 0.469  | 0.319–0.689  | <0.001 |       |              |    |
| >65                           |        |              |    |       |              |    |
| ECOG PS of TKI failure        |        |              |    |       |              |    |
| 0–1                           | 0.653  | 0.469–0.910  | 0.012 |       |              |    |
| ≥2                            |        |              |    |       |              |    |
| Subsequent treatment          |        |              |    |       |              |    |
| TKI                           | 0.566  | 0.343–0.935  | 0.017 |       |              | <0.001 |
| TKI plus                      | 0.611  | 0.385–0.971  | 0.332 |       |              | 0.192–0.573 |
| Chemo†                        | –      | –            | –  | 0.326 | 0.145–0.485  | 0.265 |
| BSC‡                          | –      | –            | –  | 0.331 | 0.220–0.498  | 0.265 |

†Reference group of subsequent treatment in Cox proportional hazards regression model of PFS. ‡Reference group of subsequent treatment in Cox proportional hazards regression model of OS. BSC, best supportive care; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI plus chemo, EGFR-TKI continuation with chemotherapy; TKI, tyrosine kinase inhibitors.
Treatment subsequent to EGFR-TKI failure  
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This study analyzed OS in 240 NSCLC patients who developed EGFR-TKI failure, including BSC. The results showed that the median OS of the EGFR-TKI continuation, EGFR-TKI continuation with chemotherapy, and chemotherapy alone groups were all superior to those of the BSC group, in which the median OS increased at least 6.9 months. Kuo et al. enrolled 114 first-line EGFR-TKI-resistant patients with advanced NSCLC, of which 67 cases received sequential chemotherapy and 47 BSC. Their results revealed that, compared with the BSC group, the median OS of the chemotherapy group increased by 7.4 months (11.2 vs. 3.8 months, \( P < 0.01 \)). Kim et al. also demonstrated that in 417 patients who benefited from gefitinib and received subsequent treatment after gefitinib failure, the survival benefit of the chemotherapy group was more significant than for the BSC group (HR = 0.38, 95% CI = 0.27–0.53). Conversely, Kim et al. found no significant difference between the EGFR-TKI continuation and BSC groups, which may be relevant to retrospective and small sample studies. Our study indicated that patients who are qualified for and capable of continuing treatment should adopt active treatment as they may achieve survival benefits.

In this study, multivariate analysis showed that EGFR-TKI as a first-line therapy is an independent predictive factor that improves efficacy and a prognostic factor that reduces disease progression. The results indicated that efficacy of and survival rates for post-progression treatment were related to initial EGFR-TKI treatments, where earlier EGFR-TKI application may result in higher control rates and longer survival benefits after EGFR-TKI failure. A PS of 0–1 at initial EGFR-TKI failure is an independent prognostic factor reducing disease progression and risk of death, where patients with a good PS at initial EGFR-TKI failure can achieve greater clinical benefits with active treatment. However, this study also showed that EGFR mutation status was not related to the efficacy of and survival rates for post-progression treatment.

This retrospective study had some limitations. Our data were from a small sample size with strong case heterogeneity. Furthermore, as cases of EGFR mutation-sensitive patients were rare, we performed no further stratified analyses.

Conclusions

This study showed that a small portion of patients with advanced lung adenocarcinoma resistant to EGFR-TKIs may benefit from the combination of EGFR-TKIs with chemotherapy, which may become a valuable therapeutic strategy for suitable patients. Patients who are qualified for and capable of continuing treatment should adopt active treatment. It is necessary to conduct future prospective and large sample studies to explore the resistance mechanism of patients who benefited from EGFR-TKI.
continuation with chemotherapy in order to screen for probable beneficiaries.

**Disclosure**

No authors report any conflict of interest.

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