

**Original**

**EGFR-TKI Versus Chemotherapy for Previously Untreated Advanced Non-Small Cell Lung Cancer in Asians : A Meta-Analysis**

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**Abstract :** We comparatively assessed the overall efficacies of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and chemotherapy for previously untreated, EGFR mutation-positive, advanced non-small cell lung cancer in Asians through a meta-analysis of relevant phase-3 trials. The primary and secondary outcomes were overall survival (OS) and progression-free survival (PFS), respectively. Pooled estimates were calculated as hazard ratios (HRs) with 95% confidence intervals (CIs). Seven studies on EGFR-TKIs met the inclusion criteria for this study. The HRs and 95% CIs for OS and PFS for EGFR-TKIs, relative to chemotherapy, were 0.98 (0.77–1.24) and 0.32 (0.24–0.43), respectively. We found no difference in overall efficacy between EGFR-TKIs and chemotherapy in terms of OS, although the median PFS with EGFR-TKI was superior to that with chemotherapy among Asians with previously untreated, EGFR mutation-positive, advanced non-small cell lung cancer (UMIN ID : UMIN28424).

**Key words :** EGFR-TKI, meta-analysis, chemotherapy, lung cancer

**Introduction**

Lung cancer is the most common cause of cancer-related death worldwide, with a 5-year survival rate of only 15%. Non-small cell lung cancer (NSCLC) affects approximately 80% of cases of lung cancer<sup>1)</sup>, and patients with advanced NSCLC generally have a poor prognosis, with a median survival time of 8–10 months<sup>1)</sup>.

Lung carcinoma cells overexpress epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors that includes Her1 (EGFR), Her2 (Erb-B2), Her3 (Erb-B3), and Her4 (Erb-B4)<sup>2)</sup>. Furthermore, mutations in the tyrosine kinase (TK) domain of EGFR have been associated with anti-apoptotic signaling<sup>3, 4)</sup> and increased sensitivity to selective EGFR-TK inhibitors (EGFR-TKIs). Several EGFR-TKIs, such as gefitinib, erlotinib, and afatinib, are now available for treatment of previously unresponsive EGFR mutation-positive, advanced NSCLC; however, the efficacy of EGFR-TKIs in terms of overall survival (OS) remains to be

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conclusively established. In particular, their efficacy in terms of OS among Asians remains to be confirmed statistically<sup>5-7)</sup>.

Several phase-3 studies have compared the efficacies of EGFR-TKIs and conventional chemotherapies<sup>8-11)</sup>, and all reported longer progression-free survival (PFS) with EGFR-TKIs. Based on these results, EGFR-TKIs are now considered the cornerstone of first-line treatment for patients with previously untreated, EGFR mutation-positive, advanced NSCLC<sup>12)</sup>, although the comparative efficacies of EGFR-TKI and conventional chemotherapies in terms of OS remain to be fully explored.

A previous study reported significantly superior OS in Asian patients with previously untreated, advanced NSCLC harboring an EGFR exon-19 deletion mutation compared to cases without such a deletion<sup>5)</sup>. In Japan, this mutation has a reported frequency of 48% in EGFR-mutated NSCLC<sup>13)</sup>; however, several studies on EGFR-TKIs showed no superiority in OS relative to conventional chemotherapy in patients with previously untreated, EGFR mutation-positive, advanced NSCLC<sup>6,7)</sup>. In the present study, we therefore statistically analyzed OS in Asian patients with previously untreated, EGFR mutation-positive, advanced NSCLC to compare the overall efficacy of EGFR-TKI treatment and conventional platinum-based chemotherapies through a meta-analysis of phase-3 randomized trials.

## **Materials and methods**

### *Literature search*

Two investigators (KA and TO) independently searched the MEDLINE (PubMed), Scopus, and Cochrane library databases for studies published up to July 2017, using the following terms: “lung cancer,” “EGFR-TKIs,” “gefitinib,” “erlotinib,” and “afatinib”, as detailed in Supplementary Table 1. No restriction was imposed on the search language, and additional relevant articles were also searched in the reference lists of retrieved articles. In cases of discrepancy between the two investigators, a third investigator (HS) performed an additional evaluation or our research team resolved the discrepancy through discussion.

### *Inclusion and exclusion criteria*

Studies were considered eligible if they met the following criteria: 1) phase-3 studies or their post-treatment analyses on the clinical efficacy of EGFR-TKIs in Asian patients diagnosed with NSCLC, and 2) studies that included OS and/or PFS as outcomes. Observational, case-control, cohort, and non-blind clinical trials were excluded. All references were independently screened by KA and TO in accordance with the inclusion and exclusion criteria.

### *Data extraction*

Relevant data from eligible studies were extracted on the basis of the predefined criteria for this meta-analysis. The primary and secondary outcomes were OS and PFS, respectively. PFS is defined as the length of time during and after disease treatment that a patient lives with the disease without worsening. According to the Response Evaluation Criteria in Solid Tumors criteria,

Table 1. Characteristics of included studies

Study, year of publication	N <sup>†</sup>	Treatments compared	n <sup>‡</sup>	Median age, years	Male subjects, n (%)	History of adenocarcinoma, n (%)
Mitsudomi <i>et al</i> 2010 <sup>9)</sup>	172	Gefitinib	86	64.0	27 (31.4%)	83 (96.5%)
		Cisplatin/ docetaxel	86	64.0	26 (30.2%)	84 (97.7%)
Maemondo <i>et al</i> 2010 <sup>8)</sup>	228	Gefitinib	114	63.9	42 (36.8%)	103 (90.4%)
		Carboplatin/ Paclitaxel	114	62.6	41 (36.0%)	110 (96.5%)
Zhou <i>et al</i> 2015 <sup>7)</sup>	154	Erlotinib	82	57	34 (41%)	72 (88%)
		Gemcitabine/ Carboplatin	72	59	29 (40%)	62 (86%)
Wu <i>et al</i> 2014 <sup>10)</sup>	364	Afatinib	242	58	87 (36.0%)	NR
		Gemcitabine/ Cisplatin	122	58	39 (32.0%)	NR
Wu <i>et al</i> 2015 <sup>11)</sup>	217	Erlotinib	110	57.5	42 (38.2%)	104 (94.5%)
		Gemcitabine/ Cisplatin	107	56.0	42 (39.3%)	101 (94.4%)
Kato <i>et al</i> 2015 <sup>5)</sup>	83	Afatinib	54	65.5	17 (31.5%)	NR
		Cisplatin/ Pemetrexed	29	66.0	9 (31%)	NR

<sup>†</sup>Number of patients from each trial included in the present meta-analysis; <sup>‡</sup>number of patients in each treatment group.

PFS is the duration until tumor size increases by 20% or until death, whichever is earlier. OS is defined as the length of time from the date of diagnosis or start of treatment until patient death.

#### Assessment of risk of bias

The Cochrane-recommended methodology<sup>14)</sup> was employed to examine each included study for potential bias arising from any of the following factors: random sequence generation; allocation concealment; blinding of participants, personnel, or outcome assessment; incomplete outcome data; selective reporting.

#### Statistical analysis

Statistical heterogeneity among the trials was assessed using  $I^2$  statistics<sup>15)</sup>, which measure the degree of heterogeneity in outcome measures by calculating the percentage of total variation among the included studies.  $I^2$  values  $\geq 50\%$  indicate significant heterogeneity. The significance of heterogeneity was tested using  $\chi^2$  statistics. Random effects models were calculated regardless of the presence or absence of statistically significant heterogeneity.

The predefined primary and secondary outcomes were comparatively assessed between the

EGFR-TKI and conventional chemotherapy groups. Pooled estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). All analyses were performed using the RevMan software (version 5.3, Cochrane Corporation, Oxford, UK).

## Results

### *Study characteristics*

The study selection process is shown in Figure 1. We identified 336 manuscripts, of which 17 remained after the removal of duplicates. After title / abstract and full-text screening, 7 reports including a total of 1,218 patients were ultimately included in the present meta-analysis<sup>5-11</sup>.

The study characteristics are listed in Table 1. The sample size ranged from 83 to 364 subjects. Three studies used gefitinib<sup>6, 9, 13</sup>, two used erlotinib<sup>7, 11</sup>, and the remaining two used afatinib<sup>5, 11</sup>. The mean patient age ranged from 56.0 to 65.5 years. The proportion of male patients ranged from 30.2% to 41%.

### *Bias assessment*

All studies exhibited a low risk of bias for all factors, except for blinding of participants and personnel in three studies. Figures 2A and 2B present the risk of bias assessments made by the present authors. None of the studies were excluded from the meta-analysis due to poor quality or a difference in baseline characteristics.

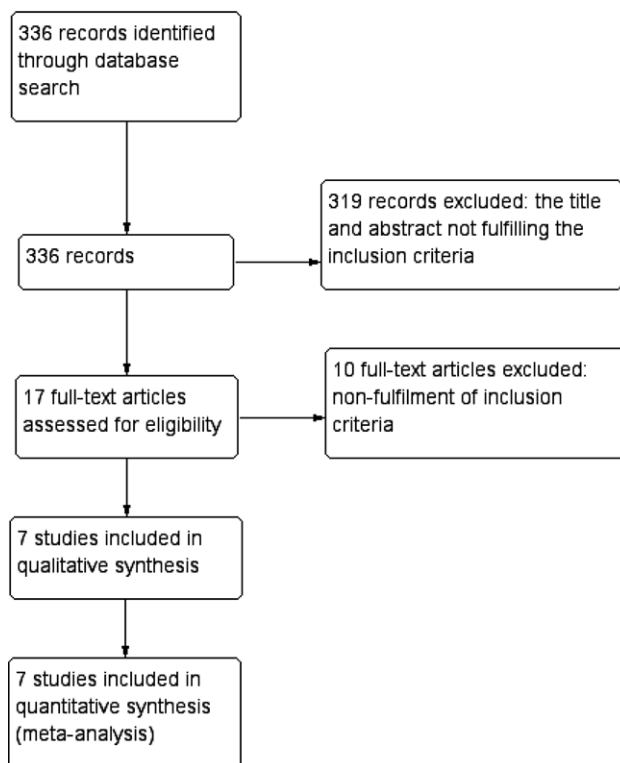


Fig. 1. Study selection process

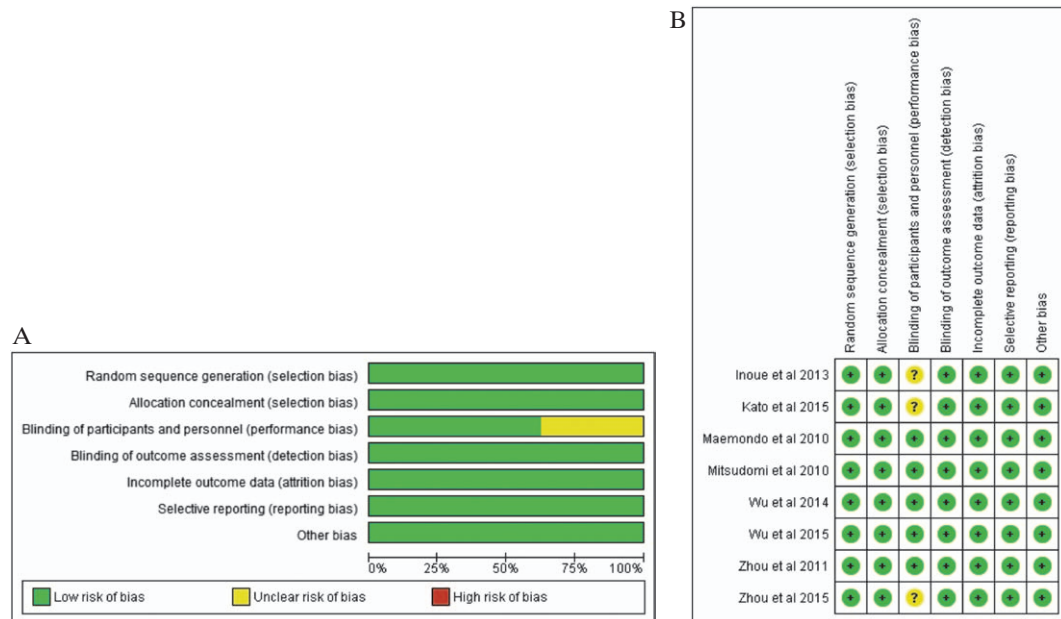


Fig. 2. Summary of bias assessment. (A) Risk-of-bias graph showing items determined by the authors as having a risk of bias (presented as percentages) in both included studies. (B) Summary of risk of bias showing items determined by the authors as presenting a risk of bias in each included study.

### Primary outcome

Three studies had comparatively assessed OS between EGFR-TKI and platinum-based chemotherapies — one study had compared OS between gefitinib and carboplatin/paclitaxel<sup>6</sup>; another had compared OS between erlotinib and gemcitabine/carboplatin<sup>7</sup>; and the third study had compared OS between afatinib and cisplatin/pemetrexed<sup>5</sup>. There was no significant inter-study heterogeneity among these studies ( $I^2 = 5\%$ ;  $P = 0.85$ ). Meta-analysis of these comparisons was performed using a random effects model. The results revealed no significant difference in OS between patients who had received EGFR-TKI treatment and those who had received platinum-based chemotherapies, with an HR of 0.98 (95% CI, 0.77-1.24; Fig. 3). The results of subgroup analysis of the exon-19 deletion and exon-21 L858R mutation subpopulations also revealed no significant differences in OS between EGFR-TKI and platinum-based chemotherapies [HRs, 0.76 (0.17-3.29) and 0.96 (0.60-1.52), respectively; Figs. 4, 5].

### Secondary outcome

Six studies had comparatively evaluated PFS after EGFR-TKI treatment and platinum-based chemotherapies<sup>5, 7-11</sup> — two studies compared gefitinib and carboplatin/paclitaxel or cisplatin/docetaxel<sup>8, 9</sup>; two other studies compared erlotinib and cisplatin/gemcitabine or carboplatin/gemcitabine<sup>7, 11</sup>; and the remaining two studies compared afatinib and cisplatin/gemcitabine<sup>5, 10</sup>. There was significant inter-study heterogeneity among these studies ( $I^2 = 68\%$ ;  $P = 0.008$ ). Meta-analysis of these comparisons was performed using a random effects model. The results revealed significantly greater PFS in patients who had received EGFR-TKI treatment than in

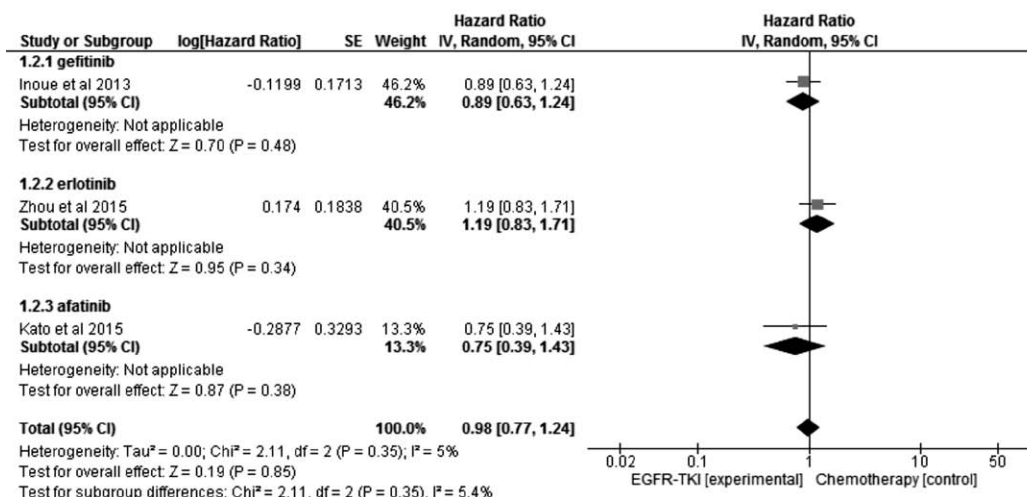


Fig. 3. Forest plot of overall survival. Comparisons between EGFR-TKIs and platinum-based chemotherapies are shown. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor ; CI, confidence interval ; HR, hazard ratio ; SE, standard error.

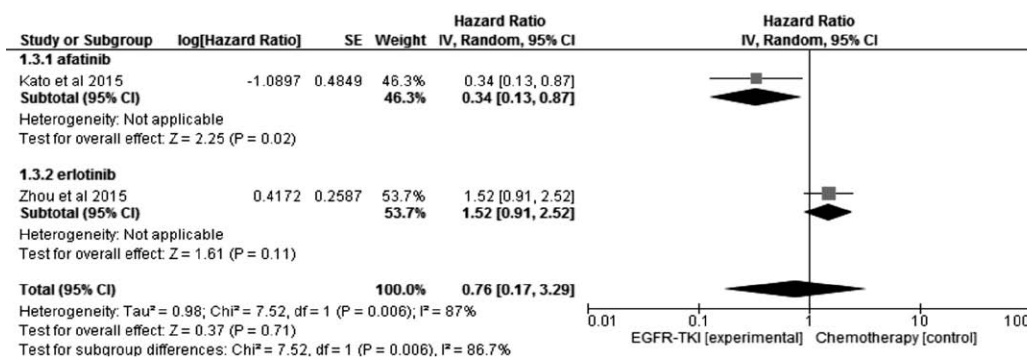


Fig. 4. Forest plot of overall survival in the subpopulation with exon-19 deletions. Comparisons between EGFR-TKIs and platinum-based chemotherapies are shown. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor ; CI, confidence interval ; HR, hazard ratio ; SE, standard error.

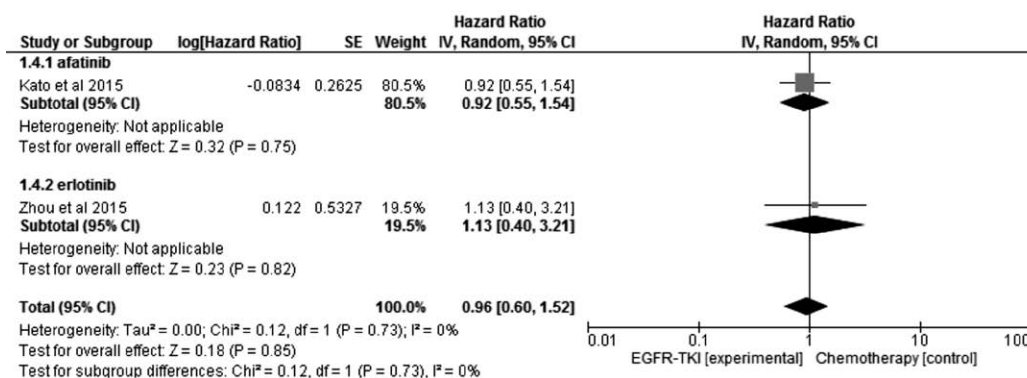


Fig. 5. Forest plot of overall survival in the subpopulation with exon-21 L858R mutations. Comparisons between EGFR-TKIs and platinum-based chemotherapies are shown. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor ; CI, confidence interval ; HR, hazard ratio ; SE, standard error.

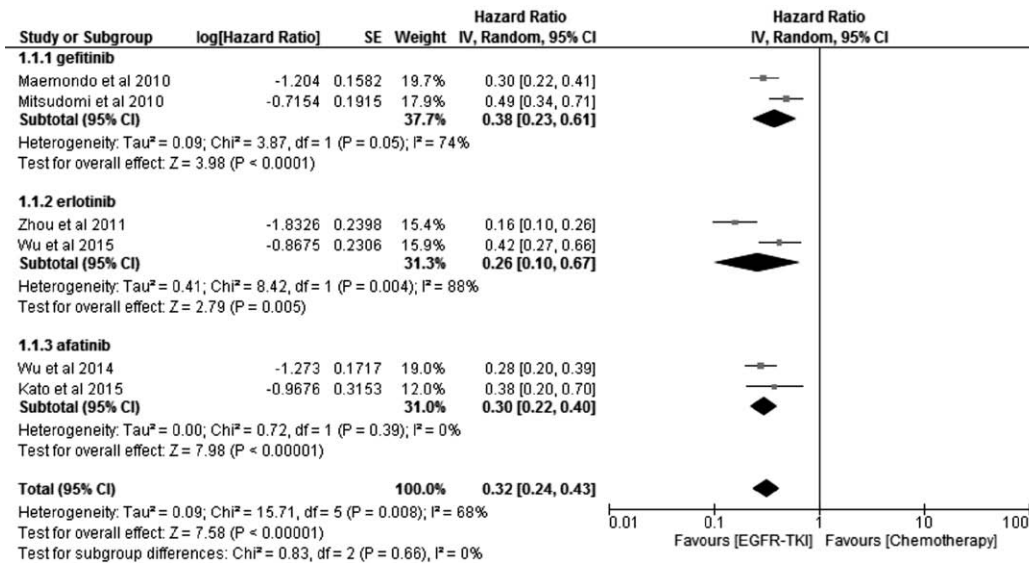


Fig. 6. Forest plot of progression-free survival. Comparisons between EGFR-TKIs and platinum-based chemotherapies are shown. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; SE, standard error.

those who had received platinum-based chemotherapy [HR, 0.32 (0.24–0.53); Fig. 6].

The results of subgroup analysis of patients who had received treatment with gefitinib, erlotinib, and afatinib also revealed a significant improvement in PFS relative to patients who had received platinum-based chemotherapy, with HRs of 0.38 (0.23–0.61), 0.26 (0.10–0.67), and 0.30 (0.22–0.40), respectively (Fig. 6).

## Discussion

In this meta-analysis, we compared the efficacies of EGFR-TKIs and conventional chemotherapy for previously untreated, EGFR mutation-positive, advanced NSCLC in Asians. The results of meta-analysis showed no significant differences in OS between the therapy groups, although patients who had received EGFR-TKIs exhibited significantly greater PFS than those who had received conventional chemotherapies.

Previous phase-3 studies had compared the efficacies of EGFR-TKI treatment and conventional platinum-based chemotherapies in similar patient groups<sup>2–8</sup>). These studies could not demonstrate the superiority of EGFR-TKI over conventional chemotherapy in terms of OS<sup>2–4</sup>), although they reported that EGFR-TKI treatment caused a significant improvement in the median PFS compared to the platinum-based chemotherapy<sup>8–11</sup>).

The results of the present meta-analysis revealed similar efficacy profiles of EGFR-TKI treatment and conventional chemotherapy as those reported in the previous phase-3 studies. Our subgroup analyses also could not demonstrate the efficacy for OS, although the previous study demonstrated that afatinib significantly improved OS in patients with NSCLC harboring exon 19 deletion (Del19) mutations. The present results do not support the theory that EGFR-TKI treatment is more effective for previously untreated EGFR-mutation-positive advanced

NSCLC than conventional platinum-based chemotherapy in terms of OS.

Previous meta-analyses have also comparatively assessed the efficacies of EGFR-TKIs and platinum-based chemotherapies<sup>8-11</sup>), with the results showing better PFS after EGFR-TKI treatment. To date, a meta-analysis of efficacy profiles involving OS (including subgroup analysis according to the type of EGFR-sensitive mutation) has not been performed, and such information would be critical for clarifying the efficacy of EGFR-TKIs in terms of OS after treatment for previously untreated, EGFR mutation-positive, advanced NSCLC. Thus, the efficacy of EGFR-TKI treatment in providing longer OS remains controversial partially because several published studies have demonstrated that EGFR-TKIs are associated with improved OS in patients with previously untreated, advanced NSCLC harboring exon-19 deletion mutations<sup>5</sup>). It has been reported that, in comparison with patients with NSCLC with L858R mutation, those with exon-19 deletion mutations tend to be younger and exhibit lymphatic metastasis, although further analyses are needed to clarify whether there are any differences in baseline clinical characteristics between these two groups<sup>16</sup>).

Several limitations of the present meta-analysis should be acknowledged. First, we only considered published studies, which might have resulted in publication bias<sup>17</sup>). Second, meta-analyses are a form of retrospective research and, as such, they are subject to the same methodological limitations as retrospective studies. For example, pharmaceutical companies supported some of the studies included in the present meta-analysis, and the authors reported receiving personal fees and grant support, potentially contributing to publication bias. Moreover, there is also a possibility of outcome selection bias. Third, we intended to assess the efficacy of EGFR-TKIs in the treatment of previously untreated, advanced NSCLC; however, the second- or third-line treatment might have varied (EGFR-TKI or chemotherapy) among patients included in the present meta-analysis. This heterogeneity of treatment after first-line treatment among the patients makes it difficult to draw any conclusions about OS. There remains an unmet medical need for further analyses to identify differences in OS between patients who have received EGFR-TKI treatment even once and those who have only received chemotherapy. Finally, we used a random effects model to account for the significant heterogeneity among the included studies, and data on heterogeneity could only be collected in part.

In conclusion, we comparatively assessed the efficacies of EGFR-TKIs and conventional chemotherapies for previously untreated, advanced NSCLC, and found no significant differences in OS, but we did find significantly greater PFS among patients who had received EGFR-TKI treatment compared to the patients who had received conventional chemotherapies. Thus, the OS advantage for patients receiving EGFR-TKI treatment even once over those treated by chemotherapy alone remains uncertain, as it does among patients with different types of EGFR-sensitive mutations. Thus, further analyses are needed to clarify the efficacy of EGFR-TKIs for treating previously untreated, advanced NSCLC and to identify subpopulations that might benefit from EGFR-TKI treatment.

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**Conflict of interest disclosure**

None of the authors have any conflict of interest to declare.

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