doi.org/10.36721/PJPS.2021.34.4.REG.1459-1468.1

REPORT

Clinical outcomes of using second – versus first-Generation EGFR-tkis for the First-Line treatment of advanced NSCLC patients with EGFR mutations: A meta-analysis

Bing Hou[#], Xiao Lu[#], Dong-Cai Gao, Quan-Xing Liu, Dong Zhou, Hong Zheng* and Ji-Gang Dai*

Department of Thoracic Surgery, Xinqiao Hospital, Army Military Medical University (Third Military Medical University), Chongqing, China

Abstract: First-generation EGFR-TKIs (gefitinib/erlotinib) and second-generation EGFR-TKI (afatinib) have become the current first-line treatments for EGFR-mutated non-small cell lung cancer (NSCLC), however, the effects of using second-generation EGFR-TKIs compared to those of using first-generation EGFR-TKIs as a first-line treatment for NSCLC patients with EGFR mutations remain unknown. We conducted this meta-analysis based on 4 retrospective and 2 randomized controlled studies published between 2016 and 2018. We surveyed the effectiveness of afatinib/dacomitinib and gefitinib/erlotinib as first-line treatments for stage III-IV EGFR-mutated NSCLC patients. The combined hazard ratio (HR) for the progression free survival (PFS) of second-generation EGFR-TKI group versus that first-generation drug group was 0.64 [95% confidence interval (95% CI) 0.55–0.74; P<0.001], demonstrating a superior PFS in the second-generation group. This outcome coincided with the subgroup analyses comparing the PFS of patients with EGFR exon 19 deletion (HR = 0.68 [95% CI 0.55–0.83; P = 0.0002]) or L858R mutation (HR = 0.64 [95% CI 0.51–0.81; p=0.0002]). Meanwhile, second-generation drugs could to significantly improve the time to progression (TTFs) compared to first-generation drugs (HR = 0.81 [95% CI 0.67–0.89; P = 0.03]). Afatinib and dacomitinib may be the superior first-line treatment for advanced NSCLC patients with EGFR mutations.

Keywords: Lung cancer, EGFR mutation, EGFR-TKI, First-line treatment.

INTRODUCTION

Lung cancer is the most common malignant tumor type and has the highest morbidity and mortality rates worldwide, and approximately 80-85% of all lung cancers are non-small cell lung cancer (NSCLC). The traditional methods of lung cancer treatment mainly include surgery, radiotherapy and chemotherapy, which are considered to have ideal curative effects on the treatment of primary lung cancer. However, most lung cancer patients have already entered the middle and late stages when their diagnoses are confirmed, and a high recurrence rate after conventional treatment leads to a poor prognosis. Only 17% of all lung cancer patients are expected to live for five years (Chen *et al*., 2016, Siegel *et al*., 2018). With the development of genome sequencing technology, the molecular mechanisms underlying tumor occurrence and progression have gradually been revealed. Cancer cells are often addicted to the sustained overexpression or activity of specific activated oncogenes for maintenance of their malignant phenotype (Weinstein 2002). According to the different "oncogene addictions", further typing the molecular basis of various gene mutations in lung cancer was performed, as targeting the treatment of critical mutations provides hope for advanced lung cancer patients, especially for those whose tumors progress after treatment.

The current clinical treatment for advanced NSCLC patients is determined by the mutation statuses of driven genes and tumor histology (Azzoli *et al*., 2011). More than half of all NSCLC patients carry a mutation in the epidermal growth factor receptor (EGFR) (Martincorena *et al*., 2015) and targeting mutant EGFR is an established approach for the treatment of patients with advanced NSCLC (Johnson *et al*., 2014). Gefitinib and erlotinib, first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs), are widely used as first-line treatments for advanced NSCLC worldwide. Although first-generation EGFR-TKIs can reversibly combine with and inhibit only one receptor of the Erb family, EGFR, the overall survival (OS) and disease-free survival rates of patients with advanced lung cancer are still improved with these drugs (Mok *et al*., 2009, Maemondo *et al*., 2010). Unlike first-generation drugs, the second-generation EGFR-TKIs, afatinib and dacomitinib can combine with and suppress four receptors of the Erb family, EGFR, ErbB2, ErbB3 and ErbB4 (Joshi *et al*., 2015). More importantly, the combination of afatinib, dacomitinib and these receptors is irreversible, indicating that second-generation drugs are

*Corresponding author: e-mail: daijigang@tmmu.edu.cn

more efficient than first-generation drugs based on their molecular characteristics (Solca *et al*., 2012, Chen *et al*., 2013). Recent studies reported better progression-free survival (PFS) rates for advanced NSCLC patients treated with afatinib and dacomitinib compared with those of patients treated with gefitinib or erlotinib (Park *et al*., 2016, Wu *et al*., 2017, Sutandyo *et al*., 2019).

Although afatinib has been considered a first-line treatment for advanced NSCLC patients with EGFR mutations (Cappuzzo *et al*., 2015, Ho *et al*., 2019, Wang *et al*., 2019, Yokoyama *et al*., 2019), the first- and second-generation drugs that are most effective for first-line treatment remain unclear. This study was carried out to compare the PFS and time to progression (TTF) outcomes of advanced NSCLC patients with EGFR mutations who received first- or second-generation EGFR-TKIs as first-line treatments. Using pooled analysis, we hoped to form a consensus about whether first- or second-generation EGFR-TKIs are superior for the first-line treatment of advanced NSCLC patients with EGFR mutations.

MATERIALS AND METHODS

Search strategy for published studies

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati *et al*., 2009). We retrieved published literature for original research by searching multiple electronic databases, including PubMed, MEDLINE, Embase, and ISI Web of Science, from their dates of inception to Jul 2018 using the following keywords related to lung cancer: WBRT, EGFR-TKIs, brain metastases and radiotherapy. The search and identification processes were independently conducted by two authors. According to a standardized approach, the decision for each study selection was reached by discussion. To maximize the search sensitivity, we implemented the following strategy: ‘‘lung cancer’’ [all fields] AND ‘‘first-line treatment’’ [all fields] AND ‘‘second-generation TKI’’ [MeSH Terms] OR ‘‘Afatinib, Dacomitinib’’ [all fields] AND ‘‘first-generation TKI’’ [MeSH Terms] OR ‘‘Gefitinib, Erlotinib’’ [all fields]. All the studies were filtered depending on inclusion and exclusion criteria.

Selection criteria

Studies meeting the following inclusion criteria were considered eligible and included in this meta-analysis: (1) all the patients included had untreated advanced NSCLC with EGFR mutation; (2) both first- and second-generation EGFR-TKIs were used as first-line treatment; (3) the study was designed according to a randomized, prospective cohort or case-control format; (4) data on PFS or TTF were provided; (5) intervention: afatinib or dacomitinib and control: gefitinib or erlotinib. Studies were excluded for the following reasons: (1) having a review, commentary, editorial, case report, or letter format; (2) both first- and second-generation EGFR-TKIs were used as second- or third-line treatments; (3) lacked key information for the calculation of methods; (4) duplicate studies in which the number of patients or length of follow-up were increased; only the most informative article was included in this meta-analysis.

Quality assessment

The included studies were qualitatively assessed according to the Newcastle-Ottawa Scale (NOS) for the quality assessment of cohort and case-control study (Zhang *et al*., 2017). A star system for the NOS (range, 0-9 stars) was developed for the evaluation. The values for the included studies are shown in table 1.

Data extraction and critical appraisal

PFS and TTF were the primary outcomes of this meta-analysis. All data used for the analysis were extracted from the included eligible articles (all available texts, tables and figs). The latest data were used when repeated cases were reported. Each retrieved article was reviewed by two independent investigators. A third expert adjudicator and discussion were utilized if discrepancies occurred between the two reviewers.

STATISTICAL ANALYSIS

The meta-analysis was performed by combining the results of the reported PFS or TTF. The log (hazard ratio) [ln (HR)] and its standard error (SE) were used as the outcome measure for the combined data. The HR and associated variance data in each included study were obtained or calculated according to the techniques described by Tierney and Stewart (Tierney *et al*., 2007). Because the HRs of PFS/TTF could not be obtained in some studies directly, data were extracted from their Kaplan–Meier survival curves to calculate the HR and SE. Data from Kaplan-Meier curves were read by Engauge Digitizer version 4.1. The calculations were performed independently by two researchers, and discrepancies were discussed until a consensus was reached.

The summary statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, United Kingdom). The heterogeneity between trials was assessed using the Chi-square statistic; an I^2 value less than 50% and a p value greater than 0.10 suggested that no statistical heterogeneity existed. The inverse variance random effects model was used when the clinical characteristics and methodology were not substantially different, when I^2 was greater than 50% and when the P value was less than 0.10. The influence of the study regarding the overall effect size was identified by sensitivity analysis.

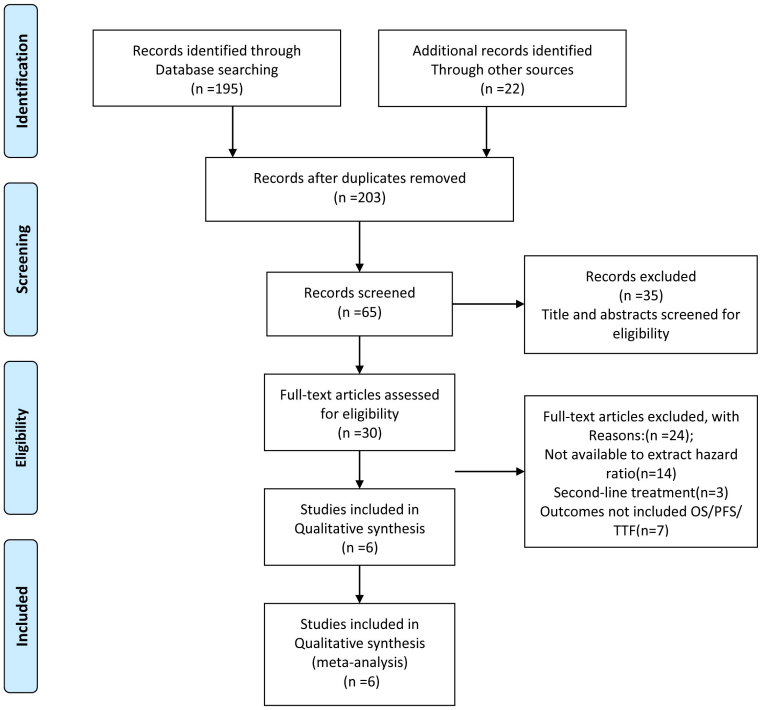

Fig. 1: Flow chart of the literature retrieval according to the PRISMA statement.

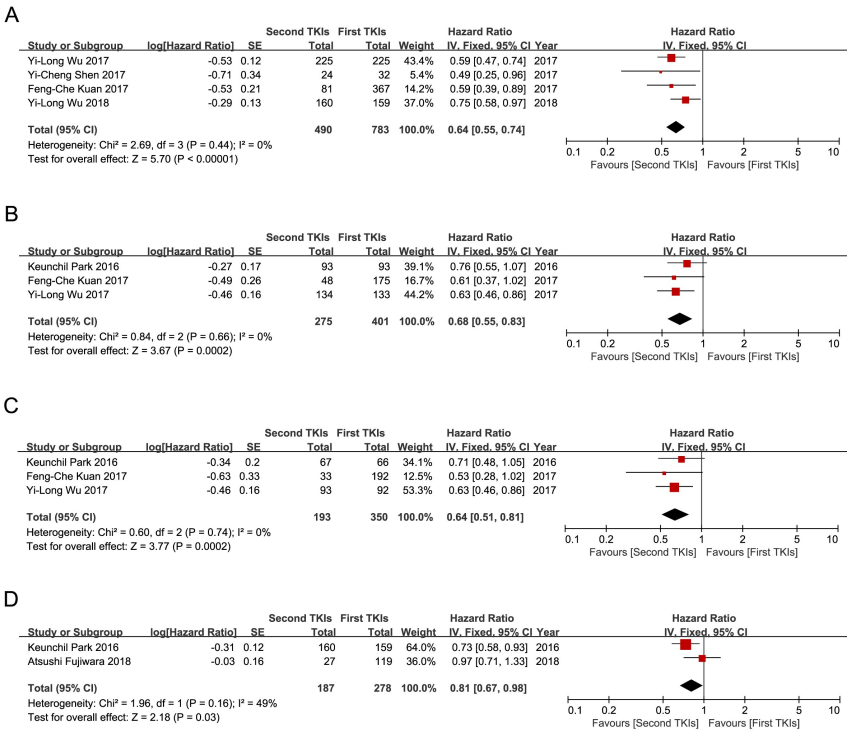

Fig. 2: (A) Forest plot of the following comparison: the PFS rates of advanced NSCLC patients with EGFR mutations treated with second- versus first-generation TKIs. Four studies were included. (B) Forest plot of the following comparison: the PFS rates of advanced NSCLC patients with an exon 19 deletion treated with second- versus first-generation TKIs. Three studies were included. (C) Forest plot of the following comparison: the PFS rates of advanced NSCLC patients with an L858R mutation treated with second- versus first-generation TKIs. Three studies were included. (D) Forest plot of the following comparison: TTFs of advanced NSCLC patients with EGFR mutations treated with second- versus first-generation TKIs. Two studies were included.

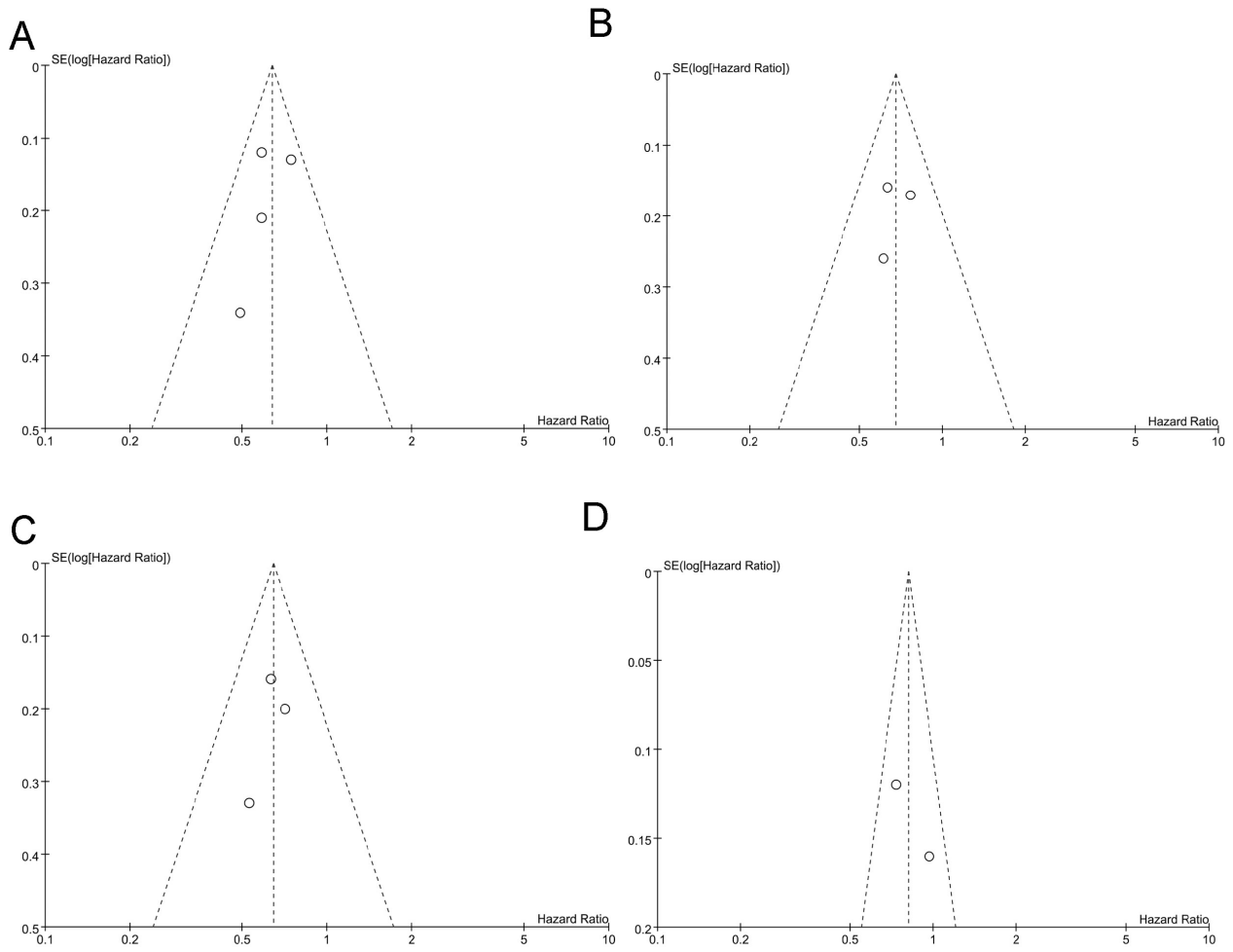

Fig. 3: (A) Funnel plot of PFS rates based on the outcomes of comparing the use of second- versus first-generation TKIs for the treatment of advanced NSCLC patients with EGFR mutations for the visual detection of systematic publication bias and small study size effects. (B) Funnel plot of PFS rates based on the outcomes of comparing the PFS rates of advanced NSCLC patients with exon 19 deletions treated with second- versus first-generation TKIs for the visual detection of systematic publication bias and small size study effects. (C) Funnel plot of PFS rates based on the outcomes of comparing the PFS rates of advanced NSCLC patients with L858R mutations treated with second- versus first-generation TKIs for the visual detection of systematic publication bias and small study size effects. (D) Funnel plot of TTFs based on the outcomes of comparing the PFS rates of advanced NSCLC patients with EGFR mutations treated with second- versus first-generation TKIs for the visual detection of systematic publication bias and small study size effects.

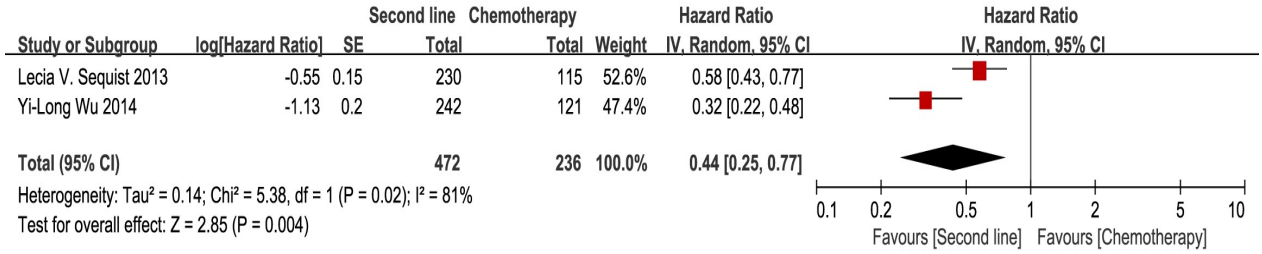

Fig. S1: Forest plot of the following comparison: the PFS rates of advanced NSCLC patients with EGFR mutations treated with second-generation TKIs versus chemotherapy. Two studies were included.

Table 1: Description of studies comparing Second-generation between First-generation TKIs

Author	Year	Second-generation vs First-generation TKIs	MST	Research Year range	Follow up (m)	Tumor stage	Age	Second-generation TKI	First-generation TKI	Race	Research type	NOS
Atsushi Fujiwara17	2018	28 vs 83 28 vs 36	13.1 vs 9.2 13.1vs 9.8	2010-2016	40	IIIA/B +IV	NA	Afatinib 40mg/d	Gefitinib 250mg/d Erlotinib 150mg/d	Japanese	Retrospective	8
Yi-Long Wu18	2018	160vs 159	14.7 vs 10.8	NA	42	IIIB+IV	NA	Afatinib 40mg/d	Gefitinib 250mg/d	Asian, White	Retrospective	7
Feng-Che Kuan19	2017	81 VS 304 81 VS 63	10.3 VS 12.1 10.3 VS 11.2	2011-2015	18	IIIB+IV	64 VS 65	Afatinib 40mg/d	Gefitinib 250mg/d Erlotinib 150mg/d	Asian	Retrospective	6
Yi-Long Wu12	2017	227vs 225	14.7 vs 9.2	2013-2015	38	IIIB+IV (88.72%)	62 vs 61	Dacomitinib 45mg/d	Gefitinib 250mg/d	Asian, White	Randomised	
Yi-Cheng Shen20	2017	21 vs 30	11 vs 3.6	2011-2016	30	IIIB+IV	NA	Afatinib 40mg/d	Gefitinib 250mg/d Erlotinib 150mg/d	Asian	Retrospective	7
Keunchil Park13	2016	160vs159	11 VS 10.9	2011-2013	42	IIIB+IV	63 vs 63	Afatinib 40mg/d	Gefitinib 250mg/d	Asian, White	Randomised	

Table 2: Subgroup analysis between Second-Generation TKIs and First-Generation TKIs

Author	Gender		Age		Smoking status		ECOG performance status		Brain metastases	Ethnic origin	
	male	female	<65	≥65	Never smoked	Former or current	0	1		Non-Asian	Asian
Feng-Che Kuan19	0.44 (0.23-0.83)	0.52 (0.30-0.92)	0.52 (0.30-0.88)	0.47 (0.23-0.96)	0.61 (0.38-0.96)	0.29 (0.11-0.81)	NA	NA	0.42 (0.16-1.05)	NA	NA
	0.55 (0.26-1.15)	0.58 (0.33-1.02)	0.60 (0.34-1.06)	0.52 (0.25-1.08)	0.52 (0.31-0.90)	0.67 (0.30-1.51)	NA	NA	0.69 (0.24-2.01)	NA	NA
Keunchil Park13	0.88 (0.59–1.31)	0.65 (0.47-0.91)	0.68 (0.48-0.97)	0.85 (0.59-1.22)	0.80 (0.58–1.10)	0.68 (0.44-1.05)	0.89 (0.54–1.47)	0.71 (0.52–0.95)	0.76 (0.41–1.44)	0.72 (0.49-1.06)	0.76 (0.54–1.06)
Yi-Long Wu12	0.72 (0.51–1.02)	0.50 (0.37–0.67)	0.51 (0.39-0.69)	0.69 (0.48–0.99)	0.51 (0.39–0.68)	0.72 (0.49-1.05)	0.65 (0.43–1.00)	0.56 (0.43–0.73)	NA	0.51 (0.39–0.66)	0.89 (0.57–1.39)
Total	0.71 (0.56-0.89)	0.56 (0.46-0.68)	0.57 (0.47-0.68)	0.70 (0.56-0.88)	0.60 (0.50-0.72)	0.66 (0.50-0.85)	0.74 (0.54-1.02)	0.62 (0.51-0.76)	0.65 (0.41-1.04)	0.57 (0.46-0.71)	0.81 (0.61-1.06)
p value	0.003	<0.001	<0. 001	0.020	<0.001	0.002	0.060	<0.001	0.070	<0.001	0.120
NA; Not Available											

Table S1: Description of studies comparing Second-generation between First-generation TKIs

Author	Year	Second line TKI vs chemotherapy	MST	Research Year range	Follow up (m)	Tumor stage	Patients' age	Second line TKI	chemotherapy	Race	Research type
Yi-Long Wu[30]	2014	242 vs 141	11.0vs5.6	2010-2011	30	IIIB+IV	58 vs 58	Afatinib 40mg/d	IV gemcitabine 1000 mg/m² on day 1 and day 8 plus cisplatin 75 mg/m² on day 1 of a 3-week schedule for up to six cycles	Asian	Randomized
Lecia V. Sequist[29]	2013	230 vs 115	11.1vs6.9	2009-2011	25	IIIB+IV	61.5 vs 61	Afatinib 50mg/d	up to six cycles of IV pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) once every 21 d	Asian and others	Randomized

Notes: IV; intravenous, NA; not available

Table S2: Subgroup analysis between Second-generation EGFR TKIs vs Chemotherapy

Author	Gender		Age		Smoking status		ECOG performance status	
	male	female	< 65	≥ 65	Never smoked	Former or current	0	1
Yi-Long Wu[30]	0.36 (0.21–0.63)	0.24 (0.16–0.35)	0.30 (0.21–0.43)	0.16 (0.07–0.40)	0.24 (0.16–0.34)	0.45 (0.23–0.88)	0.22 (0.12–0.41)	0.29 (0.20–0.43)
Lecia V. Sequist[29]	0.61 (0.37-1.01)	0.54 (0.38-0.78)	0.53 (0.36-0.76)	0.64 (0.39-1.03)	0.47 (0.33-0.67)	0.83 (0.48- 1.42)	0.50 (0.31-0.82)	0.63 (0.43-0.91)
Total	0.48 (0.33-0.69)	0.38 (0.29-0.50)	0.39 (0.30-0.51)	0.44 (0.29-0.68)	0.35 (0.27-0.46)	0.65 (0.43-0.99)	0.36 (0.25-0.53)	0.42 (0.32-0.55)
p Value	< 0.001	< 0.001	< 0.001	0.0002	< 0.001	0.05	< 0.001	< 0.001

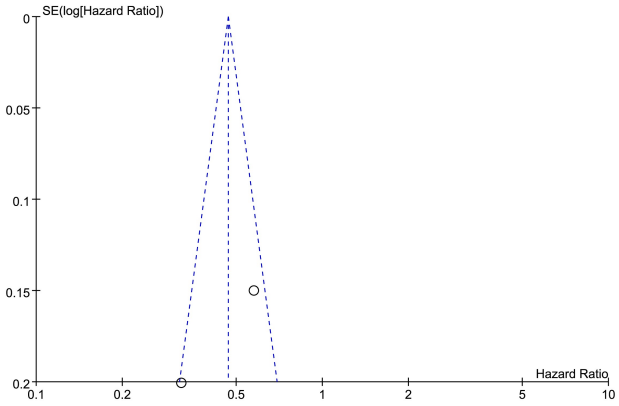

Fig. S2: Funnel plot of PFS rates on the outcomes of comparing the use of second-generation TKIs versus chemotherapy for the treatment of advanced NSCLC patients with EGFR mutations for the visual detection of systematic publication bias and small study effects.

RESULTS

Characteristics of the included trials

According to the selection criteria, six studies were included in this analysis (Park *et al*., 2016, Kuan *et al*., 2017, Shen *et al*., 2017, Wu *et al*., 2017, Fujiwara *et al*., 2018, Wu *et al*., 2018) and a total of 1738 patients were utilized to compare the efficacies of second- and first-generation EGFR-TKIs. In total, 677 and 1061 patients with advanced-stage lung adenocarcinoma with EGFR mutations who completed follow-up and were further analyzed received afatinib/ dacomitinib or gefitinib/ erlotinib, respectively. The search results and selection details are shown in fig. 1. Details regarding each study, including the publication year, number of patients included, median survival time (MST) for each group, research year, follow-up time, tumor stage at first diagnosis, treatment procedure, ethnic origin of the subjects and research type for each trial, are shown in table 1.

PFS and TTF comparisons between first- versus second-generation EGFR-TKIs

As shown in fig. 2A, among patients harboring EGFR mutations, the PFS of patients treated with second-generation EGFR-TKIs was significantly improved compared with that of patients treated with first-generation EGFR-TKIs (HR = 0.64 [95% CI 0.55-0.74; p<0.001]). This result coincided with that of the subgroup analysis that compared the PFS rates of advanced NSCLC patients with an EGFR exon 19 deletion, as subjects treated with second-generation EGFR-TKIs exhibited a PFS superior to that of subjects treated with first-generation EGFR-TKIs (HR = 0.68 [95% CI 0.55-0.83; p = 0.0002]) (fig. 2B). In the subgroup analysis of patients with the L858R mutation, the PFS of subjects treated with second-generation EGFR-TKIs was also superior to that

of subjects treated with first-generation EGFR-TKIs (HR = 0.64 [95% CI 0.51–0.81; p = 0.0002]) (fig. 2C).

When comparing the TTFs between second-generation and first-generation EGFR-TKIs, 187 patients treated with second-generation drugs and 278 patients treated with first-generation drugs reported by two studies were included,(Park *et al*., 2016, Fujiwara *et al*., 2018) and the combined HR value was 0.81 [95% CI 0.67-0.89; p= 0.03]) (fig. 2D). These pooled analyses revealed that compared with first-generation EGFR-TKIs, second-generation drugs provided advanced NSCLC patients with EGFR mutations significant PFS and TTF benefits.

Subgroup analysis of PFS

In addition to the EGFR mutation type, subgroup analysis of PFS was conducted for the gender, age, smoking status, baseline ECOG (Eastern Cooperative Oncology Group) score, brain metastasis and ethnic origin parameters of these patients. The main results outlined in table 2 demonstrated that patients of both-genders, ages and smoking histories analyzed can benefit from second-generation TKIs in terms of PFS. However, the PFS rates of patients with an ECOG score of 0, brain metastases or Asian patients did not improve regardless of whether these patients received first- or second-generation drug treatment. Although significant differences in combined HR values were observed, the p values of these groups were greater than 0.05. However, the results showed that patients with an ECOG score of 1 and non-Asian patients still benefited from second-generation TKIs.

Second-generation TKIs and chemotherapy

Another meta-analysis was performed to compare the PFS rates between patients receiving second-generation TKIs and chemotherapy. Two randomized studies (Sequist *et al*., 2013, Wu *et al*., 2014) involving 708 NSCLC patients with EGFR mutations were included in this analysis (Table S1), and the forest plot showed that patients treated with second-generation TKIs exhibited a PFS superior to that of patients treated with first-generation drugs (HR = 0.44 [95% CI 0.25-0.77; p = 0.004]) (fig. S1). Funnel plot for bias analysis was shown in fig. S2. As shown in Table S2, the subgroup analyses of gender, age, smoking status and ECOG performance status revealed that patients in any subgroup who were treated with second-generation TKIs had a better PFS than those treated with first-generation drugs, and all analysis results had statistical significance.

Sensitivity analysis and publication bias

To determine whether each individual research study overly influenced the final results, sensitivity analyses were repeated, excluding each study one at a time; no significant discrepancies in the outcomes were found. The consequences were similar regardless of whether a random or fixed-effect model was utilized. Publication bias was determined by asymmetry of the funnel plot, which was used to estimate the precision of the trials (fig. 3 and Fig S2). Each circle represents the treatment effect, expressed as the logarithm of the HR of OS in each trial plotted against the SE as a measure of study size. The perpendicular line depicts the pooled estimate of the meta-analysis. Funnel plot analysis of the OS/PFS of comparisons did not indicate significant publication bias.

DISCUSSION

NSCLC patients harboring EGFR mutations represent a molecularly distinct type of lung cancer that has established first-line treatment options; these include the first-generation EGFR-TKIs gefitinib and erlotinib and the second-generation TKI afatinib (Lynch *et al*., 2004, Paez *et al*., 2004, Sharma *et al*., 2007, Schuler *et al*., 2019). All three drugs have been approved on the basis of randomized trials showing superior PFS, objective responses, and more favorable safety profiles compared with standard first-line platinum-based doublet chemotherapy in patients with EGFR mutant NSCLC (Mok *et al*., 2009, Maemondo *et al*., 2010, Mitsudomi *et al*., 2010, Rosell *et al*., 2012, Sequist *et al*., 2013). Another second-generation EGFR-TKI, dacomitinib, was reported to generate a superior response rate (17% vs 5.3%, p=0.01) and PFS (median: 2.86 m vs 1.91 m, p= 0.01) in NSCLC patients who had not been treated with EGFR-TKIs in the past and in whom chemotherapy treatments failed compared to those of patients treated with erlotinib (Ramalingam *et al*., 2012). In a randomized, open-label, phase 3 trial (ARCHER 1050), dacomitinib significantly improved the PFS of patients with EGFR mutation-positive NSCLC compared with that of patients treated with gefitinib as a first-line treatment and should be considered as a new treatment option for this population. However, whether second-generation TKIs are more suitable for the first-line treatment of advanced NSCLC patients with EGFR mutations remains unclear. Answering this question could aid in choosing which clinical medications are administered.

The main results of this meta-analysis showed that compared with first-generation TKIs, the second-generation drugs exerted significantly superior PFS and TTF benefits. Furthermore, subgroup analysis was conducted to investigate whether the results were influenced by the different EGFR mutant types. Based on the analyzed results, regardless of whether patients harbored exon 19 deletions or L858R mutations, second-generation TKIs still yielded a superior PFS for the first time. These results suggested that the second-generation TKIs should be considered as first-line treatments for advanced NSCLC with EGFR mutations. Interestingly, another subgroup analysis showed that second-generation TKIs were no better than first-generation TKIs for the treatment of patients with an ECOG score of 0, brain

metastases or Asian patients. Although the combined HR value of first-generation drugs appeared to be better than that of second-generation drugs, no statistically significant differences were observed. Although our results showed that second-generation TKIs (afatinib) had a a superior PFS as compared with gemcitabine or pemetrexed plus cisplatin (fig. S1). Nevertheless, upon comparing OS rates between patients receiving second-generation TKIs and chemotherapy, two current trials (Yang *et al*., 2015, Wu *et al*., 2018) indicated that second-generation TKIs might not improve the OS compared with chemotherapy.

However, this study does have some limitations. First, second-generation TKIs could reportedly cause more side effects than chemotherapy (Yang *et al*., 2013), which may be related to their mechanistic features. Regrettably, not enough clinical studies are available to conduct a meta-analysis to compare the side effects of these second-generation EGFR-TKIs. Although our results showed that second-generation TKI treatment is better than first-generation TKI treatment and chemotherapy, their clinical applications might be limited by side effects. More randomized clinical trials should be conducted to investigate the optimal dosage and usage of second-generation drugs. Second, the OS rates between the two groups could not be compared in this meta-analysis because the current clinical studies did not provide enough data (Paz-Ares *et al*., 2017, Wu *et al*., 2018). However, the conclusions of two studies that reported OS rates found no survival benefit for afatinib compared with gefitinib (median: 27.9 m vs 24.5 m, p=0.2580, HR = 0.86, 95% CI 0.66-1.12, p=0.258). Interestingly, this result was consistent with that of the comparison between second-generation drugs and chemotherapy. Third, the level of evidence was relatively low, as most of the included articles were retrospective studies, and whether the clinical outcomes could have been affected by undefined bias and/or confounding factors was unclear. A total of 1738 advanced NSCLC patients with EGFR mutations were included in this analysis, but the number of patients was still small, and larger multicenter studies will be needed in the future. In the end, the third generation TKI Osimertinib was exhibited superior PFS than standard EGFR-TKIs (18.9 months vs. 10.2 months) in untreated EGFR mutation–positive NSCLC patients (Soria *et al*., 2018). However, the available articles were not enough to compare third or second generation TKI which was preferable for first-line therapy in advanced NSCLC patients with EGFR mutations.

CONCLUSION

In conclusion, this meta-analysis revealed second-generation EGFR-TKIs as first-line treatments lead to significantly high PFS and TTF rates for advanced NSCLC patients with EGFR mutations. Therefore, the first-choice therapy for advanced EGFR mutant NSCLC patients should be second-generation EGFR-TKIs when possible.

REFERENCES

Azzoli CG, Temin S, Aliff T, Baker SJ, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pao W, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D and Giaccone G (2011). 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. *J. Clin. Oncol.*, **29**(28): 3825-31.

Cappuzzo F, Finocchiaro G, Grossi F, Bidoli P, Favaretto A, Marchetti A, Valente M L, Cseh A, Clementi L, Massey D and Santoro A (2015). Phase II study of afatinib, an irreversible ErbB family blocker, in EGFR FISH-positive non-small-cell lung cancer. *J. Thorac Oncol*, **10**(4): 665-72.

Chen W, Zheng R, Baade P D, Zhang S, Zeng H, Bray F, Jemal A, Yu X Q, He J (2016). Cancer statistics in China, 2015.*CA Cancer J. Clin.*, **66**(2): 115-132.

Chen X, Zhu Q, Zhu L, Pei D, Liu Y, Yin Y, Schuler M, Shu Y (2013). Clinical perspective of afatinib in non-small cell lung cancer. *Lung Cancer*, **81**(2): 155-61.

Fujiwara A, Yoshida M, Fujimoto H, Nakahara H, Ito K, Nishihama K, Yasuma T, Hataji O, Taguchi O, D'Alessandro-Gabazza CN, Gabazza EC, Kobayashi T (2018). A retrospective comparison of the clinical efficacy of gefitinib, erlotinib and afatinib in japanese patients with non-small cell lung cancer. *Oncol Res*., **26**(7): 1031-36.

Ho GF, Chai CS, Alip A, Wahid M, Abdullah MM, Foo YC, How SH, Zaatar A, Lam KS, Leong KW, Low JS, Yusof MM, Lee EC, Toh YY and Liam CK (2019). Real-world experience of first-line afatinib in patients with EGFR-mutant advanced NSCLC: A multicenter observational study. *BMC Cancer*, **19**(1): 896.

Johnson DH, Schiller JH and Bunn PJ (2014). Recent clinical advances in lung cancer management. *J. Clin. Oncol.*, **32**(10): 973-82.

Joshi M, Rizvi SM and Belani CP (2015). Afatinib for the treatment of metastatic non-small cell lung cancer. *Cancer Manag. Res.*, **7**: 75-82.

Kuan FC, Li SH, Wang CL, Lin MH, Tsai YH and Yang CT (2017). Analysis of progression-free survival of first-line tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring leu858Arg or exon 19 deletions. *Oncotarget.*, **8**(1): 1343-1353.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.*, **339**(NA): b2700.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S,

Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J and Haber DA (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.*, **350**(21): 2129-39.

Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T (2010). Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N. Engl. J. Med.*, **362**(25): 2380-2388.

Martincorena I, Campbell P J (2015). Somatic mutation in cancer and normal cells. *Science*, **349**(6255): 1483-9.

Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K and Fukuoka M (2010). Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol*, **11**(2): 121-128.

Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA and Fukuoka M (2009). Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N. Engl. J. Med.*, **361**(10): 947-957.

Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers W R, Johnson BE and Meyerson M (2004). EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science*, **304**: 1497-1500.

Park K, Tan E H, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kolbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V and Paz-Ares L (2016). Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. *Lancet Oncol*, **17**(5): 577-589.

Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, Yang JC, Mok T, Lee KH, Lu S, Shi Y, Lee DH, Laskin J, Kim DW, Laurie SA, Kolbeck K, Fan J, Dodd N, Marten A and Park K (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Overall survival data from the phase IIb LUX-Lung 7 trial. *ANN Oncol.*, **28**(2): 270-277.

Ramalingam SS, Blackhall F, Krzakowski M, Barrios C H, Park K, Bover I, Seog HD, Rosell R, Talbot DC, Frank R, Letrent SP, Ruiz-Garcia A, Taylor I, Liang J Q, Campbell AK, O'Connell J and Boyer M (2012). Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J. Clin Oncol.*, **30**(27): 3337-3344.

Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez J M, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno M A, Terrasa J, Munoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina M A, Taron M and Paz-Ares L (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*, **13**(3): 239-246.

Schuler M, Paz-Ares L, Sequist LV, Hirsh V, Lee KH, Wu YL, Lu S, Zhou C, Feng J, Ellis SH, Samuelsen C H, Tang W, Marten A, Ehrnrooth E, Park K and Yang JC (2019). First-line afatinib for advanced EGFRm+ NSCLC: Analysis of long-term responders in the LUX-Lung 3, 6 and 7 trials. *Lung Cancer*, **133**: 10-19.

Sequist L V, Yang J C, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater S L, Orlov S, Tsai C M, Boyer M, Su W C, Bennouna J, Kato T, Gorbunova V, Lee K H, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013). Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol.*, **31**(27): 3327-3334.

Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M and Schuler M (2013). Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J. Clin Oncol*, **31**(27): 3327-3334.

Sharma SV, Bell DW, Settleman J and Haber DA (2007). Epidermal growth factor receptor mutations in lung cancer. *Nat Rev Cancer*, **7**(3): 169-81.

Shen YC, Tseng GC, Tu CY, Chen WC, Liao WC, Chen WC, Li CH, Chen HJ and Hsia TC (2017). Comparing the effects of afatinib with gefitinib or Erlotinib in patients with advanced-stage lung adenocarcinoma harboring non-classical epidermal growth factor receptor mutations. *Lung Cancer*, **110**: 56-62.

Siegel RL, Miller KD and Jemal A (2018). Cancer Statistics, 2018. *CA Cancer J. Clin.*, **68**(1): 7-30.

Solca F, Dahl G, Zoephel A, Bader G, Sanderson M, Klein C, Kraemer O, Himmelsbach F, Haaksma E and Adolf GR (2012). Target binding properties and cellular activity of afatinib (BIBW 2992), an irreversible ErbB family blocker. *J. Pharmacol. Exp. Ther.*, **343**(2): 342-50.

Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y and Ramalingam SS (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.*, **378**(2): 113-125.

Sutandyo N, Hanafi A and Jayusman M (2019). Comparison of effectiveness of gefitinib, erlotinib, and afatinib in advanced non-small cell lung cancer patients with egfr mutation positive in indonesian population. *Zhongguo Fei. Ai Za. Zhi.*, **22**(9): 562-567.

Tierney JF, Stewart L A, Ghersi D, Burdett S, Sydes MR (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**: 16.

Wang S and Li J (2019). Second-generation EGFR and ErbB tyrosine kinase inhibitors as first-line treatments for non-small cell lung cancer. *Onco. Targets Ther.*, **12**: 6535-6548.

Weinstein I B (2002). Cancer: Addiction to oncogenes the Achilles heal of cancer. *Science*, **297**(5578): 63-64.

Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, Migliorino M R, Pluzanski A, Sbar EI, Wang T, White JL, Nadanaciva S, Sandin R and Mok TS (2017). Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. *Lancet Oncol*, **18**(11): 1454-1466.

Wu YL, Sequist LV, Tan EH, Geater SL, Orlov S, Zhang L, Lee KH, Tsai CM, Kato T, Barrios CH, Schuler M, Hirsh V, Yamamoto N, O'Byrne K, Boyer M, Mok T, Peil B, Marten A, Chih-Hsin YJ, Paz-Ares L and Park K (2018). Afatinib as First-line Treatment of Older Patients with EGFR Mutation-Positive Non-Small-Cell Lung Cancer: Subgroup Analyses of the LUX-Lung 3, LUX-Lung 6 and LUX-Lung 7 Trials. *Clin Lung Cancer*, **19**(4): e465-e479.

Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi J H, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL (2014). Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label, randomised phase 3 trial. *Lancet Oncol*, **15**(2): 213-22.

Yang J C, Hirsh V, Schuler M, Yamamoto N, O'Byrne K J, Mok T S, Zazulina V, Shahidi M, Lungershausen J, Massey D, Palmer M, Sequist LV (2013). Symptom control and quality of life in LUX-Lung 3: A phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol*, **31**(27): 3342-3350.

Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai CM, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su W C, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V and Sequist LV (2015). Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.*, **16**(2): 141-51.

Yokoyama T, Yoshioka H, Fujimoto D, Demura Y, Hirano K, Kawai T, Kagami R, Washio Y, Ishida T, Kogo M, Tomii K, Okuno T, Akai M, Hirabayashi M, Nishimura T, Nakahara Y, Kim Y H, Miyakoshi C, Yoshimura K and Hirai T (2019). A phase II study of low starting dose of afatinib as first-line treatment in patients with EGFR mutation-positive non-small-cell lung cancer (KTORG1402). *Lung Cancer*, **135**: 175-180.

Zhang C and Zhu QX (2017). Allergy is associated with reduced risk of glioma: A meta-analysis. *Allergol Immunopathol (Madr)*, **45**(6): 553-559.