

RESEARCH ARTICLE

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Versus Placebo as Maintenance Therapy for Advanced Non-small-cell Lung Cancer: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background: Use of epidermal growth factor receptor inhibitors (EGFR-TKIs) is now standard for non-small-cell lung cancer (NSCLC). However, the effects of EGFR-TKIs in maintenance therapy for advanced NSCLC patients are still unclear. The present meta-analysis was performed to examine pooled data of randomized control trials (RCT) where EGFR-TKIs were compared against placebo in maintenance regimens for patients with advanced NSCLC to quantify potential benefits and determine safety. **Methods:** Several data bases were searched, including PubMed, EMBASE and CENTRAL, and we performed an internet search of conference literature. The endpoints were objective response rates (ORR), progression-free survival (PFS) and overall survival (OS). We performed a meta-analysis of the published data, using Comprehensive Meta Analysis software (Version 2.0) with a fixed effects model and an additional random effects model, when applicable. The results of the meta-analysis are expressed as hazard ratios (HRs) or risk ratios (RRs), with their corresponding 95% confidence intervals (95% CIs). **Results:** The final analysis included six trials, covering 3,758 patients. Compared with placebo, EGFR-TKIs maintenance therapy improved ORR and PFS for patients with advanced NSCLC, the difference being statistically significant ($P < 0.05$), but proved unable to prolong patients' OS. The main adverse reactions were diarrhea and rashes. **Conclusion:** EGFR-TKIs demonstrated encouraging efficacy, safety and survival when delivered as maintenance therapy for patients with advanced NSCLC after first-line chemotherapy, especially for the patients who had adenocarcinomas, were female, non-smokers and patients with EGFR gene mutations.

Keywords: EGFR-TKIs - NSCLC - maintenance therapy

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Introduction

Lung cancer is the main cause of cancer-related death, accounting for nearly 1.4 million deaths worldwide in 2008, and has an annual age standardized incidence of 45.0 per 100,000 for male and 19.9 per 100,000 for female in eastern Asia (Ferlay et al., 2010). About 85% to 90% of these patients are diagnosed as non-small-cell lung cancer (NSCLC), with most presenting at advanced or metastatic (stage IIIB or IV) stage (Lee et al., 2012). Patients with early-stage NSCLC have relatively high long-term survival rates after surgical resection, but for advanced NSCLC patients who are unsuitable for surgery, chemotherapy still is the main treatment which prolongs survival with a positive impact on quality of life. Doublet chemotherapies consisting of platinum plus one of the third-generation agents have become the

current standard regimen, the first line of chemotherapy, the third generation agents such as vinorelbine, taxanes and gemcitabine have been introduced for the treatment of malignant tumors (Ozkaya et al., 2012). Many studies have confirmed that the platinum-based of two drugs compound has resulted in high objective response rates (ORR) and progression-free survival (PFS), however, current evidence regarding long-term survival in advanced NSCLC, particularly in overall survival (OS) is limited. More than 50% advanced NSCLC patients eventually experience disease progression and require second-line therapy which provides the median survival time of 5-8 months in the selected patients (Inal et al., 2012). In recent years, the maintenance therapy has been extensively investigated as one of strategies in order to improve current clinical results in advanced NSCLC (Novello et al., 2011). Therefore, it has become focus that advanced NSCLC

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patients after first-line standard chemotherapy and with an objective tumor response or stable disease (SD) are in favor of following maintenance therapy.

The discovery of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), mainly including gefitinib and erlotinib, was a milestone in the development of non-small cell lung cancer (NSCLC) treatment (Liu et al., 2013). EGFR-TKIs have the potential to provide anti-tumor efficacy with reduced toxicity compared with the conventional cytotoxic agents. EGFR-TKIs have advantages of well safety and tolerability which were concerned during maintenance therapy in advanced NSCLC. Erlotinib, as first-line maintenance treatment in patients with advanced NSCLC whose disease has not progressed (including SD) on first-line treatment with platinum-based chemotherapy, is the second drug approved for NSCLC maintenance therapy by the U.S. Food and Drug Administration (FDA) (Cohen et al., 2010). EGFR-TKIs were also studied in several trials to test the efficacy and safety when used for advanced NSCLC patients as a maintenance therapy after first-line chemotherapy to obtained disease control. However, there are some disagreement of PFS and OS among these studies. This meta-analysis was performed to examine pooled data of randomized control trials (RCT) where EGFR-TKIs was compared against Placebo in the maintenance regimen for patients with advanced NSCLC to quantify potential benefits and determine safety.

Materials and Methods

Search Strategy

The following database was retrieved by the computer: PubMed, EMBASE and CENTRAL (the Cochrane Central Register of Controlled Trials), and we performed an internet search of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the World Conference of Lung Cancer (WCLC). The latest search was done on January 1, 2013. We used a sensitive search strategy with keywords related to non-small cell lung cancer, NSCLC, lung cancer, epidermal growth factor receptor tyrosine kinase inhibitors, EGFR-TKIs, gefitinib, erlotinib, Iressa, Tarceva, maintenance and chemotherapy. The language was limited to English. The reference lists of all retrieved articles and those of relevant review articles were also cross-referenced. All references of relevant articles were scanned and all additional studies of potential interest were retrieved for further analysis. Two reviewers analyzed the list of references and independently selected the studies.

Inclusion and exclusion criteria

The included studies met the following criteria: (1) RCT; (2) patients must be cytologically or pathologically confirmed with NSCLC and in clinical stage III-IV; (3) the studies must compare the efficacy or toxicity of maintenance therapy with EGFR-TKIs vs. Placebo after the first-line therapy (include chemotherapy, radiotherapy and other). Studies were excluded based on the following criteria: (1) non-RCT; (2) review of the literature; (3) repeat published literature; (4) the low quality of literature;

(4) when many articles relate to the same study, subject to the most recent published literature.

Literature Screening

All the documents were retrieved by two investigators independently, by using a pre-designed information extraction form. The literatures with titles and abstracts meeting the eligibility (inclusion/exclusion) criteria were selected for evaluation. For the articles of which the eligibility could not be validated by titles and abstracts, full text was reviewed. Any discrepancies between the two investigators were judged by a third party.

Date Extraction

All the date was extracted by two investigators independently. The extraction was conducted according to the following principles: (1) extraction was strictly in compliance with the rules to promote objectivity and faithful to the original literatures, so that the authenticity and accuracy of the study results would not be affected by investigators' subjective judgment; (2) both investigators participating in information extraction were asked to attend the same training course before they started their jobs; (3) before information extraction, pre-analysis was conducted on several selected representative literatures to examine the potential problems of the extraction method; (4) any discrepancies between the two investigators during information extraction were solved through negotiation or arbitrated by a third party. The information to be extracted in the present study included: (1) The basic information of articles to be included in this study, e.g. title, author, publication date, source and etc; (2) The basic information of the study subjects, e.g. gender, age, pathological types, TNM classification and etc; (3) All of the interventions received by the subjects in both test group and control group; (4) The primary endpoints, relevant adverse reactions and the main parameters to assess the methodological quality.

Quality Assessment

The methodological qualities of the clinical trials included in the present study were assessed by using Cochrane Collaboration's tool for assessing risk of bias (Armijo-Olivo et al., 2012). By using the same evaluation method, two investigators assessed, independently, the methodological qualities for all the eligible literatures; and the assessment was based on 5 different aspects, i.e. method of randomization, method of blinding, allocation concealment, drop out or lost of follow up and intentional analysis (ITT analysis). Any discrepancies were judged by a third party. The literatures with "correct or adequate" remarks in all the 5 items above were ranked Grade "A" for their qualities as they had the smallest possibility of bias; those with "undefined or unclear" remarks in 1 item or more were ranked Grade "B", implicating a moderate risk of bias; those with "incorrect or no applicable" remarks in 1 item or more were ranked Grade "C", implicating a high risk of bias.

Endpoints

(1) The short-term efficacy was divided as complete

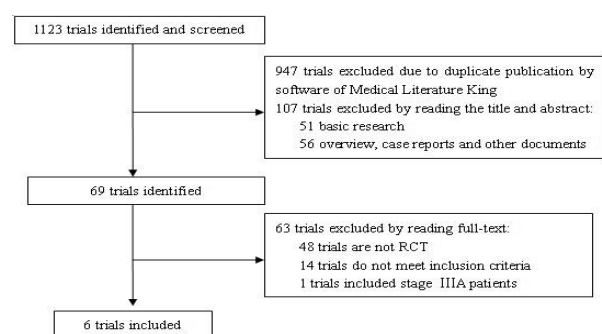
Table 1. Detailed Data of the 6 Trials Included in the Meta-analysis

Trials	Trial phase	Patients (F/M)	Histology	Stage (IIIb/IV)	Non-smoker/Smoker	First-line therapy	Maintenance therapy Experiment Control	Primary end point
Herbst 2005	III	414/654	Adenocarcinoma, Large-cell carcinoma, Squamous cell carcinoma, Other	180/898	116/962	Erlotinib or Placebo combined with up to 6 cycles of Carboplatin and Paclitaxel	Erlotinib Placebo	OS
Gatzemeier 2007	III	267/892	Adenocarcinoma, Large-cell carcinoma, Squamous cell carcinoma, Other	399/771	Unclear	Erlotinib or Placebo combined with up to 6 cycles of Gemcitabine and Cisplatin	Erlotinib Placebo	OS
Mok 2009	II	56/108	Adenocarcinoma, Other	29/125	52/102	≥1 cycle of Gemcitabine plus Cisplatin or Carboplatin and Erlotinib or Placebo in sequential combination phase	Erlotinib Placebo	NPR
Cappuzzo 2010	III	230/659	Adenocarcinoma /Bronchoalveolar carcinoma, Squamous-cell carcinoma	225/664	152/737	4 cycles of Cisplatin or Carboplatin plus Paclitaxel	Erlotinib Placebo	PFS
Gaafar 2011	III	40/133	Squamous, Adenocarcinoma, Undifferentiated, Large cell carcinoma	29/144	38/132	or Gemcitabine or Docetaxel or Vinorelbine 2-6 cycles of Platinum-based chemotherapy	Gefitinib Placebo	OS
Zhang 2012	III	121/175	Adenocarcinoma, Bronchoalveolar carcinoma, Squamous-cell carcinoma	74/221	160/136	4 cycles of Platinum-based chemotherapy	Gefitinib Placebo	PFS

F, female; M, male; NPR, non progression rate

Table 2. Quality Assessment for the Literature Included

Trials	Randomization	Allocation concealment	Blindness	Follow up	ITT analysis	Baseline	Quality grading
Herbst 2005	Yes	Unclear	Double-blind	Yes	Yes	Yes	B
Gatzemeier 2007	Yes	Unclear	Double-blind	Yes	Yes	Yes	B
Mok 2009	Yes	Yes	Double-blind	Yes	Yes	Yes	A
Cappuzzo 2010	Yes	Yes	Double-blind	Yes	Yes	Yes	A
Gaafar 2011	Yes	Unclear	Double-blind	Yes	Yes	Yes	B
Zhang 2012	Yes	Yes	Double-blind	Yes	Yes	Yes	A

**Figure 1. Flow Chart of Study Selection**

response (CR), partial response (PR), stable disease (SD) and progressive disease (PD); $ORR = (CR + PR) / \text{total cases} \times 100\%$; (2) The long-term efficacy was evaluated with respect to PFS and OS, wherein PFS referred to the time from randomization until the tumor progression or death and OS referred to the time from randomization until the death of any cause; (3) Grade 3/4 toxic reaction.

Statistical Methods

Meta-analysis was conducted on the data collected by using Comprehensive Meta Analysis software (Version 2.0). The effect sizes and 95% confidence intervals (95%CI) of ORR, PFS and OS were collaborated and analyzed, while $P < 0.05$ indicated the difference was statistically significant. The heterogeneity among the results obtained from different literatures was assessed by chi-square test. In addition, I^2 was used to quantitatively identify the degree of heterogeneity, wherein a $I^2 > 50\%$ indicated a substantial heterogeneity among the results of different studies. When inter-group heterogeneity was statistically insignificant, meta-analysis was performed by using fixed-effect model. In case that there was significant heterogeneity, the results with clinical heterogeneity were subjected to subgroup analyses, while those with non-eliminable heterogeneity were subjected to collaboration analyses by using random-effect models. If there was notably significant heterogeneity or significant

heterogeneity between the results obtained from the two groups, descriptive analysis was adopted.

Results

The results of literature retrieval and screening

In the present study, a total of 1123 papers (all in English) were sorted. By using Medical Literature King, 947 repeated entries were omitted. Through reading the titles and abstracts, 107 literatures (including 51 underlying studies and 56 narrative/case reports or other literatures) were further excluded. Sequentially, through full-text review, 59 more non-RCT articles, articles on the same topic or the articles failed to meet inclusion criteria were excluded. Furthermore, other excluded literatures were: one study covered the patients with Stage IIIA NSCLC (Kelly et al., 2008); one study (Miller et al., 2009) had the patients been treated with combined monoclonal antibody (bevacizumab) and placebo in the control group; one study (Takeda et al., 2010) had the patients been treated with platinum-based maintenance therapy as the controls and a study (Pérol et al., 2012) had the controls only received disease progression observation. As a result, only six studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010; Gaafar et al., 2011; Zhang et al., 2012) were included in the present study eventually (Figure 1).

The common characteristics of the studies included

A total of 3758 cases of patients with advanced-stage NSCLC have been investigated in the six studies, of which one was phase II clinical trial (Mok et al., 2009) and five were phase III clinical trial. In four studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010), Erlotinib was educated as the maintenance therapy; whereas Gefitinib was used for maintenance therapy in the other two studies (Gaafar et al., 2011; Zhang et al., 2012). Different first-line treatment protocols were adopted in these studies, but all of these protocols were on a basis of the combined treatment of platinum with

Table 3. Grade 3/4 Toxic Reactions

Toxic reactions	Studies	Heterogeneity		Effects model	OR(95%CI)	Z	P
		I ² (%)	P				
Neutropenia	4	0.0	0.96	Fixed	0.92 (0.79, 1.07)	1.12	0.29
Leukopenia	2	0.0	0.72	Fixed	0.88 (0.66, 1.18)	0.82	0.41
Anemia	3	58.3	0.04	Random	0.95 (0.78, 1.17)	0.29	0.77
Diarrhea	5	46.2	0.08	Fixed	3.21 (2.05, 5.04)	2.37	0.01
Rash	5	45.3	0.09	Fixed	12.35 (6.55, 23.27)	3.76	0.00

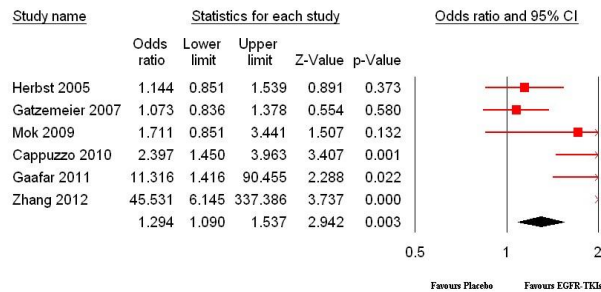


Figure 2. Meta-analysis of ORR

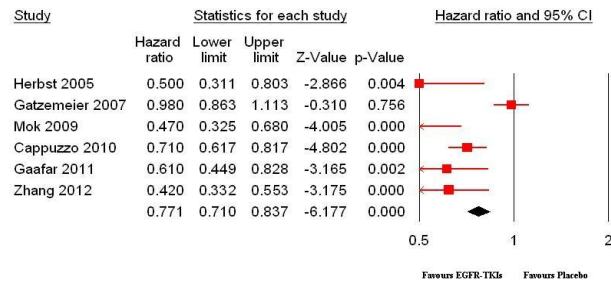


Figure 3. Meta-analysis of PFS

third-generation cytotoxic drugs (Table 1).

Quality Assessment for the studies included

All of included studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010; Gaafar et al., 2011; Zhang et al., 2012) adopted a random and controlled experimental design. Allocation concealment was employed in three studies (Mok et al., 2009; Cappuzzo et al., 2010; Zhang et al., 2012). In these studies, the patients in the control groups were treated with placebo, indicating a correct method of blinding. And the enrolled subjects were followed on a long-term basis, and all the experimental results were subjected to ITT analysis. Hence, three studies (Mok et al., 2009; Cappuzzo et al., 2010; Zhang et al., 2012) were ranked “A” for the quality, while the others (Herbst et al., 2005; Gatzemeier et al., 2007; Zhang et al., 2012) were ranked “B”, indicating the reliability of comprehensive evaluation meta-analysis was acceptable (Table 2).

Objective Response Rate

All of the six studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010; Gaafar et al., 2011; Zhang et al., 2012) have reported the respective ORR. The result of collaboration analysis showed a heterogeneity among the various studies (I²=53.2%, P<0.05), and thus random effect model was employed for the analysis. In the meta-analysis, EGFR-TKIs maintenance therapy was proved to improve ORR for the patients with advanced NSCLC, and the difference

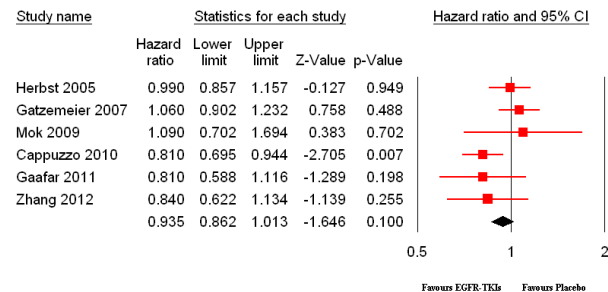


Figure 4. Meta-analysis of OS

was statistically significant (OR=1.29, P<0.01, 95%CI = 1.10-1.54) in comparison to placebo (Figure 2).

Progression-free Survival

All six studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010; Gaafar et al., 2011; Zhang et al., 2012) have reported PFS date. The result of collaboration analysis showed no heterogeneity among the various studies (I²=27.1%, P>0.05), and thus fixed effect model was employed for the analysis. In the meta-analysis, EGFR-TKIs maintenance therapy was able to prolong PFS of patient with advanced NSCLC, the difference was statistically significant (HR=0.77, P<0.01, 95%CI =0.71-0.84) in comparison with placebo. In the subgroup, the patients with advanced NSCLC (main the adenocarcinoma, female, the non-smokers and the patients with EGFR gene mutation) would be benefited from EGFR-TKIs maintenance therapy (Figure 3).

Overall Survival

All six included studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Cappuzzo et al., 2010; Gaafar et al., 2011; Zhang et al., 2012) have reported the respective OS. There was no significant heterogeneity in the HR of individual trials (I²=6.1%, P>0.05), and thus fixed effect model was employed for the analysis. In the meta-analysis, EGFR-TKIs maintenance treatment of advanced NSCLC patients did not significantly reduce the risk of disease death in comparison to placebo (HR = 0.94, P = 0.10, 95%CI = 0.86-1.01) (Figure 4).

Grade 3/4 toxic reactions

When compared with the patients with advanced NSCLC who did not receive maintenance therapy, the patients received EGFR-TKIs maintenance therapy presented increased incidences of Grade 3/4 diarrhea and rash, the difference has statistically significant (P<0.05) (Table 3).

Funnel Plots

Funnel plots was plotted on results obtained from the

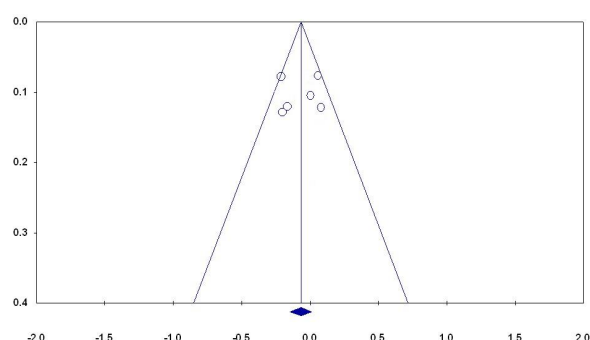


Figure 5. Funnel Plot

Meta analysis of OS. The results showed that all points were evenly scattered on both sides of the effective line, depicting a symmetric inverted funnel shape above the funnel. Most of the points were located within the range of 95%CI, suggesting a relatively smaller bias existed in the present study; in particular, publication bias was well managed (Figure 5).

Discussion

Nowadays, one of the hotspots in the treatment of NSCLC is how the advanced NSCLC patients would be benefited from the maintenance therapy of medicating well-tolerated, low-toxicity and highly efficacious drugs after achieving OR or SD at the initial first-line chemotherapy. Maintenance therapy refers to the continuous medication for the patients who have finished the complete cycles of chemotherapy and achieved the maximal tumor management outcomes (Rinaldi et al., 2006). The drugs used in the maintenance therapy for NSCLC could be either one of the drugs prescribed in the induction chemotherapy protocol or another drug with lower toxicity and no cross tolerance. The dosage of such drugs is normally very low. The duration of maintenance therapy is normally from the end of first-line therapy until the forced discontinuance due to disease (NSCLC) progression or occurrence of intolerable toxic reactions (Grossi et al., 2007). Up to date, although there is still a lot of controversy regarding the use of maintenance therapy, the concept still earns plenty of attention due to its great potential in delaying NSCLC recurrence and extending patient's survival (Quan et al., 2010). In particular, the clinical application of molecular targeted drug, which features the specific targeted action and slight adverse reaction, is believed to promise a bright perspective for the maintenance therapy in the treatment of NSCLC. In the present Meta-analysis, the use of EGFR-TKIs as the maintenance therapy for NSCLC was thoroughly analyzed and investigated, in terms of protocol design, efficacy evaluation, safety and toxic/adverse reaction.

EGFR, a member from Erb-B family of transmembrane glycoprotein receptors, is prominently over-expressed in the presence of NSCLC, most commonly in adenocarcinoma (40.0%). When the ligands bind to the extra-cellular region of the receptor, EGFR will be transformed to its homologous or heterologous dimer form, in which the intra-cellular TK region will be sequentially activated, inducing tyrosine phosphorylation and the activation of

the downstream signaling pathway, and thus resulting in abnormal cellular proliferation/differentiation, enhanced angiogenesis and inhibited apoptosis of tumor cells (Ciardiello et al., 2008). At the moment, the most widely applied EGFR-TKIs in the clinical practice are Erlotinib and Gefitinib. On both of these two drugs, several RCTs regarding the treatment of advanced-stage NSCLC have been published. However, the outcomes and results of these trials were quite different, especially the effects of EGFR-TKIs maintenance therapy on OS of the patients with advanced NSCLC were in dispute. As one of the main endpoints, PFS is more advantageous than OS in terms of being able to omit the influence of the further treatment given to the patients after disease progression. There were six studies included in our Meta-analysis, only one study (Gatzemeier et al., 2007) showed that the patients with advanced NSCLC did not have improved PFS after receiving EGFR-TKIs maintenance therapy; where in the other five studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Gaafar et al., 2011; Zhang et al., 2012), the patients OS were not varied, suggesting that OS were not benefited from the prolonged PFS. Therefore, by employing the method of Meta-analysis, the efficacy of EGFR-TKIs maintenance therapy in the treatment of advanced-stage NSCLC was evaluated on a larger sample scale. The results of our study demonstrated much improved PFS in advanced-stage NSCLC patients after receiving EGFR-TKIs maintenance therapy, i.e., the risk of disease progression for the patients with advanced-stage NSCLC was reduced.

Similarly, OS obtained from the results of 6 included studies were also inconsistent. The results of five studies (Herbst et al., 2005; Gatzemeier et al., 2007; Mok et al., 2009; Gaafar et al., 2011; Zhang et al., 2012) suggested that the patients' OS did not improve after receiving EGFR-TKIs maintenance therapy, whereas only one study (Cappuzzo et al., 2010) (Sartum study) reported a significant prolongation of OS in the advanced NSCLC patients who received Erlotinib as maintenance therapy. In this study, the median PFS of the patients in the Erlotinib group (150 mg/d, n =438) and placebo group (n=451) were 12.3 and 11.1 weeks, respectively (HR=0.71, 95% CI =0.62-0.82, $P<0.0001$), and the median OS of the two groups were 12 months and 11 months ($P=0.0088$). For the patients with EGFR gene mutation, the benefits obtained from Erlotinib treatment was more prominent ($P<0.0001$), even the patients with wild-type EGFR mutation could have improved survival. Based on this result, FDA has approved Erlotinib as the maintenance treatment of locally advanced or metastatic NSCLC (Xiao et al., 2011; Lu et al., 2011; Wu et al., 2012). In the present Meta-analysis, although improved OS in the patients with advanced NSCLC was observed in one study (Cappuzzo et al., 2010), the results of collaboration analysis showed that EGFR-TKIs maintenance treatment was unable to prolong patients' OS, and the risk of mortality has not been reduced.

The major limitation in this Meta-analysis was the heterogeneity existed among the results of different included studies, especially in the ORR and OS. The reasons for such high heterogeneity may include: (1) the

first-line therapy regimens adopted by the various studies were different, exerting a significant influence on the patients' short-term efficacy. (2) The detailed survivals (in terms of mean±SD) has not been reported in the various included studies; and thus HR and its 95%CI was collaborated for analysis during information extraction, resulting in a certain degree of measurement bias. (3) As some of the studies adopted a relatively smaller sample size, the variability among the individuals may cause inconsistency among the results of different studies; and thus the general pattern may not be well reflected. (4) Asians, females, non-smokers and NSCLC patients with adenocarcinoma were more responsive to EGFR-TKIs treatment. Among the studies included in the present Meta-analysis, two of them (Mok et al., 2009; Zhang et al., 2012) only targeted Asians as the subjects. When compared with similar the studies conducted on Caucasians, the final effect sizes of these studies were affected since the studies recruited the patients more responsive to EGFR-TKIs therapy.

Indeed, it is fact that not all the patients with advanced NSCLC need maintenance therapy, as some of the patients may achieve long-term disease remission through induction chemotherapy and some others may seek re-treatment after the disease progresses. Therefore, the selection of appropriate patients becomes the major bottleneck of the current study (Pérol et al., 2011; Velez et al., 2012; Yuan et al., 2012). At the moment, the decision of conducting maintenance therapy mainly depends on patient's requirement, the relevant symptoms of the disease, patient's performance status and their response to the first-line treatment. For the patients with higher intention or better performance status, maintenance therapy is recommended. In contrast, the patients with poorer performance status have only slim chance to be benefited from the maintenance therapy (Galetta et al., 2010). In case of using EGFR-TKIs for maintenance therapy, the selection of appropriate patients should be more careful, as a number of parameters should be taken into consideration, e.g. the mutation states and histological types of EGFR, the potential adverse reactions and etc (Reckamp, 2012). Hence, for the patients highly responsive to induction chemotherapy, targeted drug is considered more preferable when used in maintenance therapy, as such drugs feature higher tolerance. The various RCTs and the present meta-analysis showed that, in the treatment of patients with advanced NSCLC, EGFR-TKIs maintenance treatment was proved to be able to improve both ORR and PFS. However, the improvement in patients' OS is still a controversial issue. To validate this problem, further multi-center and large sample RCTs with more rationale and more rigorous designs are required in the future.

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