The Efficacy of Combining EGFR Monoclonal Antibody With Chemotherapy for Patients With Advanced Nonsmall Cell Lung Cancer

A Meta-Analysis From 9 Randomized Controlled Trials

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Abstract: Although epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) have been proved synergistic effect when combined with cytotoxic agents for advanced nonsmall cell lung cancer (NSCLC), the results of relevant clinical trials remain controversial. The purpose of this meta-analysis was to assess the advantage and toxicity profile of chemotherapy plus EGFR-mAbs versus chemotherapy alone for patients with NSCLC.

We rigorously searched electronic databases for eligible studies reporting EGFR-mAbs combined with chemotherapy versus chemotherapy alone for advanced NSCLC. The primary outcome was overall survival (OS). Pooled results were calculated using statistical methods.

Nine phase II/III randomized controlled trials involved a total of 4949 participants were included. In general, compared with chemotherapy alone, the addition of EGFR-mAbs significantly improved OS (hazard ratio [HR] = 0.91, 95% confidence interval [CI]: 0.86–0.97, P = 0.006), progression-free survival (HR = 0.83, 95% CI: 0.87–0.98, P = 0.01), response rate (odd ratio [OR] = 1.28, 95% CI: 1.12–1.47, P = 0.0003), and disease control rate (OR = 1.17, 95% CI: 1.01–1.36, P = 0.04). Subgroup analysis showed that apparent OS benefit present in patients with squamous NSCLC (HR = 0.83, 95% CI: 0.74–0.93, P = 0.001), and those treatment-naive population (HR = 0.88, 95% CI: 0.82–0.95, P = 0.006). Several manageable adverse events were markedly increased by EGFR-mAbs, such as acne-like rash, infusion reactions, and diarrhea. The risk for some >Grade 3 toxicities, such as leukopenia, febrile neutropenia, and thromboembolic events were slightly increased by the addition of EGFR-mAbs. In general, the toxicities of the combination strategy were tolerable and manageable. The addition of EGFR-mAbs to chemotherapy provided superior clinical benefit along with acceptable toxicities to patients with advanced NSCLC, especially those harboring squamous cancer and treatment-naive. Further validation in front-line investigation, proper selection of the potential benefit population by tumor histology, and development of prognostic biomarkers are warranted for future research and clinical application of EGFR-mAbs.

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Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity, ALK = anaplastic lymphoma linase, AP = pemetrexed plus cisplatin, CI = confidence interval, CTLA-4 = cytotoxic T-cell lymphocyte antigen-4, DCR = disease control rate, Doc = docetaxel, EGFR = epidermal growth factor receptor, GC = gemcitabine plus carboplatin, GP = gemcitabine plus cisplatin, HR = hazard ratio, mAbs = monoclonal antibodies, NP = cisplatin with gemcitabine, NSCLC = nonsmall cell lung cancer, OR = odd ratio, ORR = objective response rate, OS = overall survival, Pem = pemetrexed, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RCTs = randomized controlled trials, TC = taxane plus carboplatin.

INTRODUCTION

For patients with advanced nonsmall cell lung cancer (NSCLC), the efficacy of chemotherapeutic has reached “therapeutic plateau” with a median overall survival (OS) of around 8 to 10 months.1–2 Despite the fact that the prognosis of patients with epithelial growth factor receptor (EGFR) or anaplastic lymphoma linase (ALK) positive mutation is significantly improved by targeted therapies, more than half of the patients without known driver mutations have no choice for target thera-_pies mentioned above.3–6 Therefore, novel treatment strategies for patients with advanced NSCLC are still urgently required. Since aberrant function of the EGFR pathway is vital in the development of NSCLC,7–8 and the expression rate of EGFR is relatively high (40% to 80%) in NSCLC,10–11 another kind of EGFR-targeting agents, including cetuximab, panitumumab, matuzumab and more recently, necitumumab, classified as...
monoclonal antibodies (mAbs), have been currently under extensive investigation.12–15 They have shown impressive activity when combined with radiation therapy and the potential to increase the effectiveness of some cytotoxic agents have been confirmed by preclinical data.8,16

Previous clinical trials have shown that the addition of EGFR-mAbs to platinum-based chemotherapy is both tolerable and feasible.17,18 However, other clinical trials, including recent study INSPIRE, failed to validate this conclusion.19–21 These conflicting results impede the interpretation and translation of EGFR-mAbs to clinical practice. Therefore, we conducted this systemic review and meta-analysis to evaluate the efficacy and safety of the addition of EGFR-mAbs to chemotherapy, compared with chemotherapy alone in patients with advanced NSCLC. Predefined subgroup analysis was conducted to identify the potential proper patient population.

**METHODS**

Search Strategy and Study Selection

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. No ethical approval and patient consent are required as all analysis were based on previous published studies.

We systematically searched the electronic databases including PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library (between inception to January 1, 2015), as well as the meeting records related to lung cancer from ASCO and ESMO databases (2010 to January 1, 2015). The keywords used in the literature search include “chemotherapy,” “NSCLC,” “cetuximab,” “necitumumab,” “panitumumab,” “matuzumab,” and “combination.”

The purpose of this meta-analysis was to evaluate the efficacy and toxicity profile of standard chemotherapy plus EGFR-mAbs, compared with chemotherapy alone. Therefore, only randomized controlled trials (RCTs) that met the following criteria were included: Prospective phase II or III RCTs designed for patients with advanced NSCLC. Randomized assignment of participants to EGFR-mAbs (cetuximab, necitumumab, panitumumab, or matuzumab) plus standard chemotherapy as experimental group or the corresponding chemotherapy as control group. No concurrent or sequential radiotherapy is allowed during the trial. Among the included trials, 17–21,23 seven trials9,10,17–21,19,23 were investigation in front-line, while the rest were second-line trial.20,22 Two RCTs9,17 conducted in selected population according to the expression of EGFR (immunohistochemical method, IHC). Two studies18,21 selected patients according to histological type. Furthermore, 4 agents (cetuximab,9,10,17,19,20 necitumumab,18,21 panitumumab,23 or matuzumab)22 with comparable data were identified. Only 3 studies17,18,2 began with OS as the primary outcome. All studies were designed with 2 arms except one50 phase III trial, which evaluated the efficacy and toxicity of the combination of cetuximab with docetaxel or pemetrexed, compared with docetaxel or pemetrexed alone. As regard histological type, 4 studies17–21 provided relevant subgroup information. The specific number of included study may vary according to

**RESULTS**

**Study Characteristics**

Figure 1 shows the flow chart reflecting the selection process for eligible RCTs. Among the potentially eligible trials, 9 studies with 4949 patients met the inclusion criteria after rigorously identification. Other potential eligible studies were excluded for reasons of single-armed, without chemotherapy combination or involved of radiotherapy. Among the included studies, there were 5 phase III RCTs.17–21 Seven trials9,10,17–19,21,23 were investigation in front-line, while the rest were second-line trial.20,22 Two RCTs9,17 conducted in selected population according to the expression of EGFR (immunohistochemical method, IHC). Two studies18,21 selected patients according to histological type. Furthermore, 4 agents (cetuximab,9,10,17,19,20 necitumumab,18,21 panitumumab,23 or matuzumab)22 with comparable data were identified. Only 3 studies17,18,21 were designed with OS as the primary outcome. All studies were designed with 2 arms except one50 phase III trial, which evaluated the efficacy and toxicity of the combination of cetuximab with docetaxel or pemetrexed, compared with docetaxel or pemetrexed alone. As regard histological type, 4 studies17–21 provided relevant subgroup information. The specific number of included study may vary according to

**Assessment of Risk of Bias in Included Studies**

For each included study, we assessed the risk of bias following the Cochrane Collaboration guidelines (http://www.cochrane.de). Six domains were employed for this part including sequence generation, allocation concealment, blinding of participants or outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

**Statistical Analysis**

Heterogeneity across studies was assessed with a forest plot and the inconsistency statistic (I²). A random-effects model was employed in case of the existence of potential heterogeneity (I² ≥ 50%); otherwise, the fixed-effect model would be applied. We calculated the pooled hazard ratio (HR) for survival outcomes (PFS, OS) and pooled odd ratio (OR) for dichotomous data (ORR, DCR) with proper algorithm. Graphical funnel plots were generated to visually inspect for publication bias. All calculations were performed using Review Manager (version 5.2 for Windows; the Cochrane Collaboration, Oxford, UK). P < 0.05 was considered statistically significant for all analysis.
the corresponding outcomes. All of the included studies provided outcomes about OS, PFS, and ORR. Data for DCR were available in 7 trials. Complete characteristics of selected trials were summarized in Table 1.

Risk of Bias

All the eligible trials reported “randomization” and 3 studies provided the conduction details of the randomization. All of the included studies were marked with “open-label,” however, given the fact that the outcomes were assessed by independent reviewers, the risk for blinding of participants or outcome assessment were defined as “unclear risk of bias.” Moreover, for most studies included in these meta-analyses, low risk of bias existed for other key domains, including incomplete outcome data, selective outcome reporting and other sources of bias. In general, no high risk of bias was detected as shown in Figure S1, http://links.lww.com/MD/A388.

Primary Outcome: OS

In general, the median OS of patients treated with EGFR-mAbs plus chemotherapy was superior to those treated with chemotherapy alone (HR = 0.91, 95% confidence interval [CI]: 0.86–0.97, \( p = 0.006 \)). The result was shown in Figure 2. No significant heterogeneity was detected among the studies included for OS analysis (\( I^2 = 15\% \)).

Seven studies provided the detailed analysis in chemotherapy-naive patients. The median OS were 8.3 to 12.0 months for the combination group, compared with 7.3 to 11.5 months among the chemotherapy alone group in first-line setting. The pooled HR for OS was 0.88 (95% CI: 0.82–0.95, \( p = 0.0006 \)) in favor of the addition of EGFR-mAbs to the first-line standard chemotherapy. However, it failed to provided additional survival benefit in second-line setting. The pooled HR was 1.03 (95% CI: 0.88–1.17, \( p = 0.66 \)) according to the subgroup data of 2 studies.\(^{20,22}\)

As shown in Figure 3, the addition of EGFR-mAbs to chemotherapy produced a significant OS improvement for patients with squamous cancer (HR = 0.83, 95% CI: 0.74–0.93, \( p = 0.001 \)). The risk of death was decreased 17% by combination with EGFR-mAbs. Similarly, there were 3 studies provided the result of the adenocarcinoma subgroup. However, this group population only got slightly survival improvement from the addition of EGFR-mAbs and the pooled HR was 0.95 (95% CI: 0.85–1.07, \( p = 0.43 \)).

Secondary Outcomes: PFS, ORR, DCR, and Serious Adverse Effects

There was a favorable trend for the addition of EGFR-mAbs to the present standard chemotherapy in PFS, ORR, and DCR. As shown in Figure 4, the risk of disease progression was slightly but significantly decreased by 7% compared with the control group (pooled HR was 0.93, 95% CI: 0.87–0.98, \( p = 0.01 \)). Meanwhile, the addition of EGFR-mAbs to chemotherapy also significantly improved the ORR (pooled OR was 1.28, 95% CI: 1.12–1.47, \( p = 0.0003 \)) and DCR (pooled OR was 1.17, 95% CI: 1.01–1.36, \( p = 0.04 \)). Detailed description can be found in Figures 5 and 6.

All of the included studies reported the serious adverse effects. We analyzed the adverse events by preferred terms and composite categories as shown in Table 2. In general, the addition of EGFR-mAbs was tolerable and manageable. Serious adverse effects for patients receiving chemotherapy plus EGFR-mAbs were mainly acne-like rash (weighted rate: 10.39% vs 0.18%; OR 41.00, 95% CI: 18.25–92.08, \( P < 0.0001 \)), infusion-related reactions (weighted rate: 4.56% vs 0.81%, OR 4.83, 95% CI: 1.94–12.01, \( P = 0.0007 \)) and diarrhea (weighted rate: 4.03% vs 1.86%, OR 2.17, 95% CI: 1.33–3.52, \( P = 0.002 \)). Besides, the risk for some \( \geq \)Grade 3 toxicities, such as leukopenia, febrile neutropenia, and thromboembolic events also slightly increased by the addition of EGFR-mAbs, compared with chemotherapy alone. The combination regimens did not significantly increased the incidence of neutropenia, anemia, or fatigue.

Publication Bias

Highly sensitive search strategy and rigorous inclusion criteria have been applied to minimize the potential publication bias. Furthermore, according to the funnel plot conducted for assessment of publication bias, no significant asymmetry was detected for our primary outcome (Figure 7).

DISCUSSION

Nowadays, the role of EGFR as a therapeutic target has been well established. There are rational basis for EGFR mAbs to be combined with chemotherapy for advanced NSCLC in clinical practice. First, effective anti-EGFR-mAbs compete with endogenous ligands, primarily EGF, for receptor ligand-binding sites. This competitive binding blocks critical signaling pathways and suppress the growth of tumors expressing EGFR, which does not usually happen when TKIs are used.\(^{24}\) Second, preclinical research reveals that some EGFR mAbs can induce immunological reaction through antibody-dependent cell-mediated and complement-dependent pathway and enhance the cytotoxic effect of chemotherapy.\(^{24,25}\) However, results of clinical trials evaluating the effectiveness of addition of EGFR-mAbs to chemotherapy were controversial. Our meta-analysis confirmed that the addition of EGFR-mAbs to chemotherapy resulted in prolonged OS, progression-delaying effect, better response rate, and DCR than standard chemotherapy.

To our knowledge, our study is the first meta-analysis to collect data of all available RCTs on EGFR-mAbs combined with chemotherapy. Pujol et al\(^{26}\) had performed a meta-analysis of individual patient data from randomized trials of chemotherapy plus cetuximab as first-line treatment. However, our study included all the available EGFR-mAbs agents (cetuximab, nectitumumab, panitumumab, and matuzumab) and relevant high-quality RCTs to further explore the efficacy of EGFR-mAbs combined with standard chemotherapy. Yang et al\(^{27}\) also conducted a meta-analysis on similar subject, which found that the OS, 1-year survival rate, and ORR with chemotherapy plus cetuximab were apparently better than those with chemotherapy alone, but the differences in PFS were not significant. Our study, nevertheless, confirmed the apparent greater progression-delaying effect of addition of EGFR-mAbs. Possible explanation for this inconsistency was that another 5 RCTs were incorporated and the number of participant was doubled in our meta-analysis, the potential improvement trend in PFS was therefore demonstrated.

At present, there is no robust evidence for selecting the potential benefit population from EGFR-mAbs treatment by tumor histology. Results of recent studies implied that patients with squamous NSCLC might gain benefit from EGFR-mAbs. INSPIRE is a phase III RCT about the pemetrexed and cisplatin plus necitumumab (a second-generation recombinant human immunoglobulin G1 EGFR-mAbs that competitively inhibits...
| Study     | Author and Year | Phase Line | Study Arms | Number of Patients | Caucasian Origin, % | Histology | Primary Outcome | PFS (month) | OS (month) | ORR, DCR, % |
|-----------|-----------------|------------|------------|-------------------|---------------------|-----------|-----------------|-------------|------------|-------------|
| BMS100    | Butts 2007      | II 1       | Cetuximab + GP/GC | 65               | 83.1                | Unselected | ORR             | 5.09 vs 4.21 | 11.99 vs 9.26 | 27.7 vs 75.4 |
|           |                 |            | GP/GC alone | 66               | 83.3                | Unselected | P = 0.23        | P = 0.41    | 18.2 vs 74.2 | NA          |
| LUCAS     | Rosell 2008      | II 1       | Cetuximab + NP | 43               | 100                 | Unselected but EGFR-expressing | ORR         | 5.0 vs 4.6 | 8.3 vs 7.3 | 35 NA |
| FLEX      | Pirker 2009      | III 1      | Cetuximab + NP | 557              | 84                  | Unselected but EGFR-expressing | OS          | 4.8 vs 4.8 | 11.3 vs 10.1 | 36 NA |
| BMS 099   | Lynch 2010       | III 1      | Cetuximab + TC | 568              | 85                  | Unselected | PFS             | 4.40 vs 4.24 | 9.69 vs 8.38 | 25.7 vs 68 |
| SELECT    | Kim 2013         | II 2       | Cetuximab + Pem | 338              | 88                  | Unselected | PFS             | 2.9 vs 2.3 | 6.9 vs 7.8 | 72 vs 52   |
|           |                 |            | TC alone     | 338              | 88                  | Unselected | P = 0.23        | P = 0.169 | 17.2 vs 62.7 | NA          |
|           |                 |            | Pem alone    | 301              | 89                  | Unselected | PFS             | 2.9 vs 2.3 | 6.9 vs 7.8 | 72 vs 52   |
|           |                 |            | Cetuximab + Doc | 304              | 87                  | Unselected | P = 0.76        | P = 0.86 | 4 vs 48 |
|           |                 |            | Doc alone    | 167              | NA                  | Unselected | PFS             | 2.4 vs 1.5 | 5.8 vs 8.2 | 8 vs 72   |
|           |                 |            | NA           | 166              | NA                  | Unselected | P = 0.39        | P = 0.31 | 7 vs 72 |
| SELECT    | Schiller 2010    | II 2       | Muzumab + Pem | 62               | 85                  | Unselected | ORR             | 2.3 vs 2.7 | 12.4 vs 7.9 | 16 vs 36 |
|           |                 |            | Pem alone    | 51               | 92                  | Unselected | P = 0.87        | P = 0.18 | 4 vs 35 |
| NA        | Crawford 2013    | II 1       | Panitumumab + TC | 112              | 90                  | Unselected | TTP             | 17.6 vs 18.3 weeks | 37 vs 35 weeks | 15.2 vs 71 |
| SQIRE     | Thatcher 2014    | III 1      | Necitumumab + GP | 545              | 84                  | Squamous cancer | OS          | 5.7 vs 5.5 | 11.5 vs 9.9 | 31 vs 82 |
| INSPIRE   | Paz-Ares 2015    | III 1      | Necitumumab + AP | 548              | 83                  | Non-squamous NSCLC | OS          | 5.6 vs 5.6 | 11.3 vs 11.5 | 31 vs 73 |

DCR = disease control rate; EGFR = epidermal growth factor receptor; GP refers to gemcitabine (1250 or 1000 mg/m² IV, days 1 and 8) plus cisplatin (75 mg/m² IV, day 1) every 3 weeks; GC means gemcitabine plus carboplatin (AUC = 5, IV, day 1) every 3 weeks; NP for cisplatin (80 mg/m², day 1) with vinorelbine (25 mg/m², days 1 and 8) every 3 weeks; NSCLC = nonsmall cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TC means taxane/carboplatin chemotherapy, including paclitaxel (200 or 225 mg/m² IV, day 1) or docetaxel (75 mg/m² IV, day 1) plus carboplatin (AUC = 6, IV, day 1) every 3 weeks; Pem and Doc separately refers to pemetrexed (500 mg/m²) and docetaxel (75 mg/m²) IV, day 1, every 3 weeks; AP means pemetrexed (500 mg/m²) plus cisplatin (75 mg/m²) IV, day 1, every 3 weeks. All of the chemotherapy regimens were limited to 4 to 6 cycles; TTP = time to progression.
ligand binding) as first-line therapy in patients with advanced nonsquamous NSCLC.\textsuperscript{21} This study fails to prove the efficacy benefit of necitumumab plus pemetrexed and cisplatin chemotherapy for above population setting. However, in study SQIRE, a similar trial designed for patients with squamous NSCLC, the addition of necitumumab to gemcitabine/cisplatin regimen produced significant OS and PFS improvement.\textsuperscript{18} Our study also found that patient harboring squamous NSCLC were the potential population to benefit from the addition of EGFR-mAbs (HR = 0.83, 95% CI: 0.74–0.93, \(P = 0.001\)) while those with adenocarcinoma were not (HR = 0.95, 95% CI: 0.85–1.07, \(P = 0.43\)). There are 2 explanations for this finding. First, it has...
been reported that the expression rate of EGFR is higher in patients with squamous-cell compared with nonsquamous-cell carcinomas.28 Meanwhile, further analysis of study FLEX based on prospectively collected data indicated only high EGFR expression (IHC score ≥200; score 0–300) could predict survival benefit associated with the addition of cetuximab to chemotherapy.17 Second, as the genomic complexity of squamous NSCLC is much more complicated than lung adenocarcinoma,29 the immunogenicity might be stronger in former subset. A recent study found that the stronger immunogenicity of squamous NSCLC led to better response to ipilimumab treatment than nonsquamous subset.30 Therefore, it is

TABLE 2. Pooled ORR and 95% CI for Adverse Events by Preferred Terms and Composite Categories

| Adverse Events by Preferred Terms and Composite Categories | Chemotherapy Plus EGFR mAbs, Event/Total | Chemotherapy Alone, Event/Total | Odds Ratio, 95% CI | P Value | Heterogeneity, % |
|-----------------------------------------------------------|---------------------------------------|--------------------------------|-------------------|---------|-----------------|
| Neutropenia                                                | 647/1626                              | 610/1642                       | 1.18 (0.95–1.48)   | 0.14    | 36              |
| Leukopenia                                                 | 308/1258                              | 232/1264                       | 1.50 (1.23–1.84)   | <0.0001 | 0               |
| Febrile neutropenia                                        | 141/1229                              | 104/1237                       | 1.47 (1.12–1.94)   | 0.006   | 37              |
| Fatigue                                                    | 184/1696                              | 132/1653                       | 1.37 (0.99–1.90)   | 0.06    | 37              |
| Anemia                                                     | 135/1271                              | 143/1280                       | 0.95 (0.74–1.23)   | 0.71    | 0               |
| Diarrhea                                                   | 54/1341                               | 24/1291                        | 2.17 (1.33–3.52)   | 0.002   | 27              |
| Acne-like rash                                             | 232/2232                              | 4/2194                         | 41 (18.25–92.08)    | <0.0001 | 0               |
| Septic events                                              | 19/840                                | 4/851                          | 4.89 (1.66–14.45)   | 0.004   | 0               |
| Thromboembolic events                                      | 80/1256                               | 42/1217                        | 1.80 (1.22–2.64)    | 0.003   | 0               |
| Infusion-related reactions                                 | 56/1229                               | 10/1237                        | 4.83 (1.94–12.01)   | 0.0007  | 27              |

CI = confidence interval; EGFR = epidermal growth factor receptor; ORR = objective response rate.
reasonable to assume that patients with squamous NSCLC may obtain more benefit from EGFR mAbs therapy due to the function of antibody-dependent cell-mediated cytotoxicity and complement activation.

Although robust evidence favor the addition of EGFR-mAbs to chemotherapy for treatment-naive patients, whether the addition of EGFR-mAbs is of value in second-line setting remains unknown. Therefore, we provided preliminary analysis based on 2 included studies to answer this question. In contrast to first-line setting, our result indicated that combination of EGFR-mAbs with standard second-line chemotherapy failed to provided additional survival benefit (pooled HR was 1.03, 95% CI: 0.88–1.17, $P = 0.66$). The underlying mechanism is still unclear. It is noteworthy that patients’ tolerability to treatment usually deteriorated after they failed from first-line chemotherapy. According to the result of SELECT study, the toxic effects were significantly worse for the cetuximab plus chemotherapy group than for the chemotherapy group alone in the second-line setting.32 This might compromise the potential benefit from the additional EGFR-mAbs treatment. Furthermore, the chemotherapy regimen given to the majority of patients in these 2 trials was single-agent pemetrexed. However, a preclinical study found anticancer synergy between cetuximab and docetaxel, gemcitabine, cisplatin, rather than pemetrexed.31 Therefore, ineffectiveness of the synergy between cetuximab and docetaxel, gemcitabine, cisplatin/vinorelbine might also lead to the negative result in OS.

Given the safety concerns, our study revealed that serious adverse effects (≥Grade3) for patients receiving chemotherapy plus EGFR-mAbs were mainly acne-like rash, infusion-related reaction, diarrhea, leukopenia, febrile neutropenia, and thromboembolic. The combination regimens did not significantly increased the incidence of neutropenia, anemia, or fatigue. This toxicity profile of combination of EGFR-mAbs with chemotherapy was consistent with those described in previous reports. In general, the safety profile of this combination was acceptable and manageable according to original studies.

The present meta-analyses are limited by the heterogeneity of various agents employed in the individual trials. Besides, our work was not based on individual patient data. Other limitations include publication status as ongoing studies were ineligible for inclusion. However, here we presented the first meta-analysis illustrating the clinical efficacy of combining EGFR-mAbs with chemotherapy over chemotherapy alone based on available data from recent 9 RCTs.

**CONCLUSION**

The addition of EGFR-mAbs to chemotherapy could provide superior clinical benefit to patients with advanced NSCLC, especially those harboring squamous cancer and in first-line setting. Further validation in front-line investigation, proper selection of the potential benefit population by tumor histology, and development of prognostic biomarkers are warranted for future research and clinical application of EGFR-mAbs.

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