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Efficacy of Next-Generation EGFR-TKIs in Patients With Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: The efficacy of next-generation epidermal growth factor receptor-tyrosine kinase inhibitors in patients with advanced non-small cell lung cancer who have failed first-generation epidermal growth factor receptor-tyrosine kinase inhibitors still remains under investigation. **Objective:** The aim of this meta-analysis was to systematically assess the efficacy and safety profiles of next-generation epidermal growth factor receptor-tyrosine kinase inhibitors in patients with advanced non-small cell lung cancer who failed first-generation epidermal growth factor receptor-tyrosine kinase inhibitors. **Methods:** We performed a comprehensive search of several electronic databases up to September 2018 to identify clinical trials. The primary end point was overall survival, progression-free survival, disease controlled rate, objective response rate, and adverse events. Epidermal growth factor receptor-tyrosine kinase inhibitor emergent severe adverse events (grade $\geq$ 3) were analyzed. Odds ratio along with 95% confidence interval were utilized for main outcome analysis. **Results:** In total, we had 3 randomized controlled trials in this analysis. The group of next-generation epidermal growth factor receptor-tyrosine kinase inhibitors had significantly improved progression-free survival (odds ratio = 0.34, 95% confidence interval = 0.29-0.40, $P < .00001$), as well as objective response rate (odds ratio = 10.48, 95% confidence interval = 3.87-28.34, $P < .00001$) and disease controlled rate (odds ratio = 6.03, 95% confidence interval = 4.41-8.25, $P < .00001$). However, there was no significant difference in overall survival with next-generation epidermal growth factor receptor-tyrosine kinase inhibitors (odds ratio = 1.05, 95% confidence interval = 0.85-1.31, $P = .66$). Meanwhile, the odds ratio for treatment-emergent severe adverse events (diarrhea, rash/acne, nausea, vomiting, anemia) between patients who received next-generation epidermal growth factor receptor-tyrosine kinase inhibitors and those who received first-generation epidermal growth factor receptor-tyrosine kinase inhibitors did not show safety benefit ($P > .05$). **Conclusions:** Next-generation epidermal growth factor receptor-tyrosine kinase inhibitors were shown to be the better agent to achieve higher response rate and longer progression-free survival in patients with non-small cell lung cancer as the later-line therapy for previously treated patients with first-generation epidermal growth factor receptor-tyrosine kinase inhibitors. Meanwhile, they did not achieve benefit in overall survival and safety compared with the chemotherapy group. Further research is needed to develop a database of all *EGFR* mutations and their individual impacts on the various treatments.

Keywords

NSCLC, EGFR-TKIs, pretreated patients, meta-analysis

Abbreviations

AE, adverse events; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; NCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCTs, random control trials.

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Introduction

Lung cancer remains the primary cause of cancer-related death in the world.[1] Non-small cell lung cancer (NSCLC) comprises approximately 80% to 85% of all lung cancers. More than half of NSCLC cases are diagnosed at the advanced-stage with poor prognosis and are candidates for palliative adjuvant chemotherapy. Recent advances in genetic discoveries in NSCLC and the employment of specific inhibitors against them have played a key role in patients with disease at these stages.[2]

Epidermal growth factor receptor (*EGFR*) mutations, such as exon 19 deletions (Ex19Del) and the exon 21 point mutation, L858R, are powerful predictive markers for response to EGFR tyrosine kinase inhibitors (TKIs) in advanced-stage NSCLC, which have been accepted as the standard of care in this setting. [3]

As first-generation TKIs, gefitinib and erlotinib have consistently shown superior therapeutic efficacy and more favorable safety profiles than chemotherapy in patients who have a driver mutation in the *EGFR* gene for first-line therapy.[4-6] However, some studies have reported that the presence of the T790M variant reduces binding of first-generation EGFR-TKIs to the ATP-binding pocket of EGFR, which have potentially led to disease progression.[7,8]

Numerous genetic mutations have been identified as resistance mechanisms, and specific inhibitors are being developed against them. Next-generation TKIs, including second-generation TKIs (such as afatinib) and third-generation TKIs (osimertinib), have offered a potential alternative for patients who progressed after first-generation EGFR-TKI treatment.[2]

Based on positive results from prospective trials in patients whose disease had progressed on first-generation EGFR-TKI, next-generation TKIs were used to maximize the effect on delaying disease progression. Today, the efficacy of next-generation EGFR-TKIs in patients with advanced NSCLC who failed first-generation EGFR-TKIs still remains to be fully investigated. We performed this meta-analysis by including relevant trials, which have been designed to determine the efficacy and toxicity of EGFR-TKIs and focus primarily on whether next-generation EGFR-TKIs were superior in patients with NSCLC previously treated with first-line EGFR-TKI therapy.

Methods

Search Strategy

We conducted a systematic screening process using PubMed, Embase, and Cochrane Database of Systematic Reviews from their inception to September 2018, based on the MeSH terms and free key words: "non small cell lung cancer" AND "EGFR-TKIs" AND "pretreated patients". Literature was also searched using reference lists and materials.

Study Selection Criteria

Articles that were related to the following inclusion criteria were included in this analysis: (1) studies were designed as random control trials (RCTs), (2) trials focused on comparing next-generation EGFR-TKIs and chemotherapy, (3) patient with treatment-refractory advanced NSCLC after failure of first-generation EGFR-TKIs, (4) the outcomes were efficacy (overall survival [OS], progression-free survival [PFS], and tumor response) and toxicity (incidence of severe adverse effects), (5) full texts were available.

Quality Assessment

Two investigators separately assessed the quality of the retrieved studies. Study quality was evaluated using the Cochrane Collaboration's "Risk of bias" tool.

Data Extraction

Two authors independently extracted the relevant data from each trial. Disagreement was settled through discussion. We extracted the main categories based on the following: first author's family name, publication year, treatment regimen, number of patients, mean age, and end point of interests. We extracted the corresponding hazard ratios and risk ratios with 95% confidence interval (95%CI) to describe the end points of interest data.

Statistical Analysis

We performed the meta-analysis by pooling the results of OS, PFS, disease controlled rate (DCR), objective response rate (ORR), and adverse events (AEs). We utilized the Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford) to perform all statistical analyses. Chi-square test was used to assess the significance of heterogeneity, which was then examined through the I^2 statistic.[9] The fixed-effects model was used if the assessment of heterogeneity was insignificant ($I^2 \leq 50\%$). If the source of heterogeneity was not insignificant ($I^2 > 50\%$), we used the random effects model for further analysis. A P value less than .05 was considered statistically significant.

Results

Overview of Literature Search and Study Characteristics

Totally, 376 articles were identified initially. During the preliminary screening of abstracts and titles, 8 publications were further included because of the exclusion criteria. At last, a final total of 3 RCTs[10-12] were assessed for eligibility in the meta-analysis (Figure 1). All included studies in this study were based on high-quality evidence. Figure 2 shows the risk of bias summary; Table 1 provides a brief description of these 3 studies.

Clinical and Methodological Heterogeneity

Pooled analysis of PFS comparing next-generation EGFR-TKIs versus chemotherapy. In the analysis of the rate of PFS, all studies were

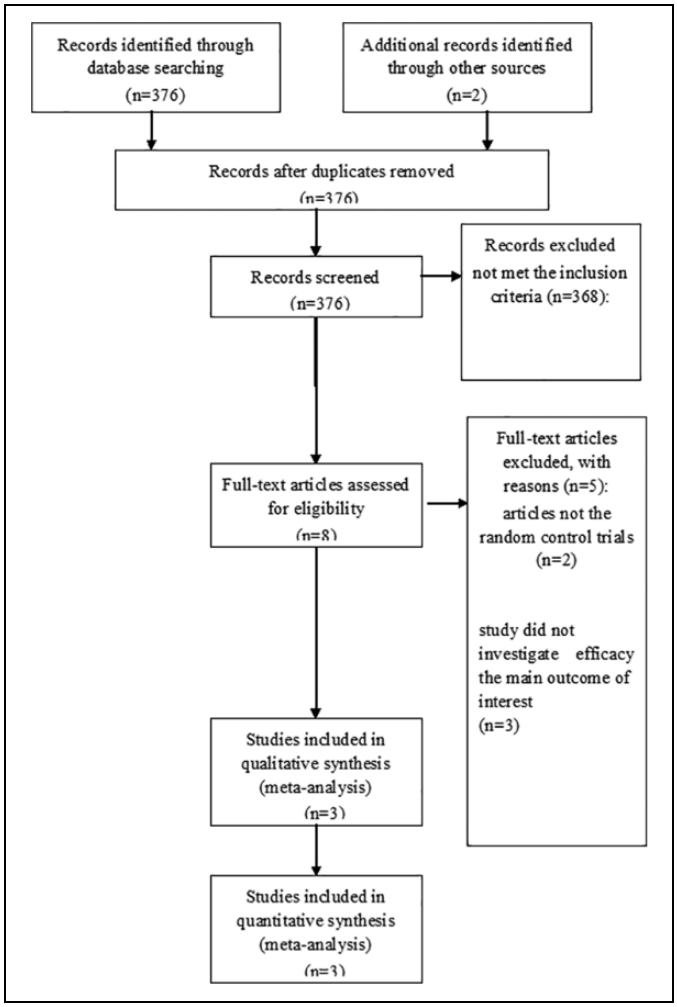

Figure 1. PRISMA flow chart of the selection process to identify studies eligible for pooling.

included, and the data are shown in Figure 3. The results showed that a significant difference in benefit was found between next-generation EGFR-TKIs and chemotherapy (odds ratio = 0.34, 95%CI = 0.29-0.40, $P < .00001$).

Pooled analysis of OS comparing next-generation EGFR-TKIs versus chemotherapy. Only 2 trials reported data on OS. As displayed in Figure 4, the pooled estimates of effect sizes showed no significant statistical difference in OS between the 2 groups (odds ratio = 1.05, 95%CI = 0.85-1.31, $P = .66$).

Pooled analysis of ORR comparing next-generation EGFR-TKIs versus chemotherapy. The random-effects model was used to pool the data on ORR since the heterogeneity across the all studies was significantly high. The pooled data showed a significant difference in advantage between the 2 groups (odds ratio = 10.48, 95%CI = 3.87-28.34, $P < .00001$). In other words, next-generation EGFR-TKIs increased the ORR (Figure 5).

Pooled analysis of AEs comparing next-generation EGFR-TKIs versus chemotherapy. We defined grade 3/4 toxicities as severe AE. Data on diarrhea, rash/acne, nausea, vomiting, and anemia were included, and are shown in Figure 6. Meanwhile, all the above data did not reach a statistically significant level ($P > .05$).

Pooled analysis of DCR comparing next-generation EGFR-TKIs versus chemotherapy. The pooling DCR data did show advantage in the next-generation EGFR-TKIs group (odds ratio = 6.03, 95%CI = 4.41-8.25, $P < .00001$).

Discussion

Epidermal growth factor receptor tyrosine kinase inhibitors are accepted as first-line therapy in NSCLC harboring mutations in *EGFR*. Nonetheless, the majority of patients eventually progress.[13,14] To our knowledge, acquiring resistance refers to disease progression after response to EGFR-TKI treatment.[15,16] Nowadays, lacking effective treatment for patients with NSCLC with an activating *EGFR* mutation after development of acquired resistance to first-generation EGFR TKIs is a major clinical problem.[17,18]

Researchers have focused on multiple resistance mechanisms for patients who acquired resistance to first-generation EGFR-TKIs.[21] These mechanisms include secondary mutations of the driver oncogene, and the activation of new signaling pathways other than the EGFR pathway.[15,20]

With resistance developed in patients who received previous first-generation EGFR TKIs, next-generation TKIs have drawn all the attention based on the positive results from previous trials in patients who have progressed after first-generation EGFR-TKI. Unlike reversible first-generation EGFR TKIs, second-generation TKIs (afatinib) is an irreversible ErbB-family blocker.[21] Moreover, osimertinib, a third-generation, irreversible EGFR TKI inhibits primary EGFR-TKI sensitizing and secondary EGFR T790M resistance mutations.[8,19,22]

The primary results of our study further supported the conclusion. Our analysis did not show difference between the groups in terms of OS, although the results of PFS and response rate were promising. In Miller's study, since 39% patients were still alive, as the trial was post hoc analyzed in February 2012, no benefit was found in OS between the groups. Consistent with the similar results, statistical significance was not achieved in Nie's study.

The effect on survival efficacy seemed to be associated with specific *EGFR* mutations, which might potentially separate patients into different biological categories. Patients treated by afatinib and osimertinib have different predictive and prognostic impacts with Del19 and L858R mutations in EGFR.[7,19,23,24] A retrospective study reported that compared with the L858R-positive disease treated with osimertinib, the prevalence of secondary T790M mutation was associated with better response in del19-positive disease. [25] Meanwhile, *in vitro* and *in vivo* study with afatinib, the activating *EGFR* mutations models, including L858R and deletion-19, and the exon 20 gatekeeper T790M mutations, with less benefit.[7,19] In the future, studies comparing the

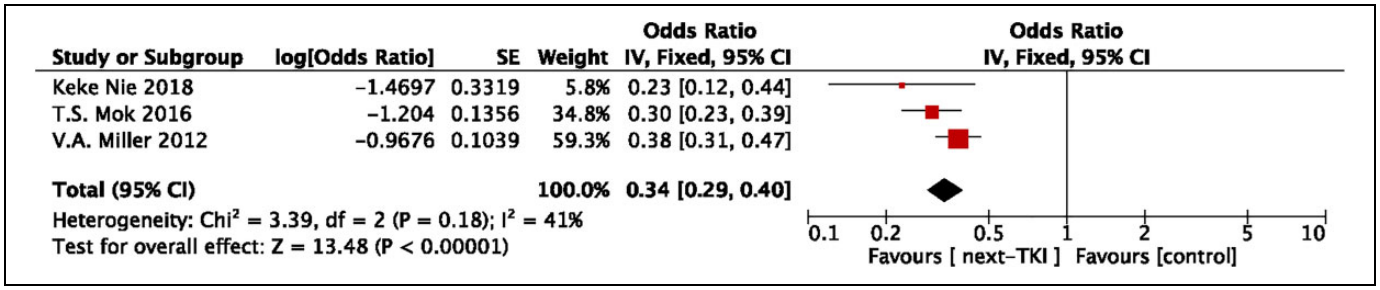

Figure 2. Pooled analysis of PFS comparing next-generation EGFR-TKIs versus chemotherapy. EGFR-TKI indicates epidermal growth factor receptor-tyrosine kinase inhibitors; PFS progression-free survival.

Table 1. Detailed Description of Included Trails.

		Treatment regimen		Patients number		Age (years)	
Study	Year	Study arm	Comparative arm	Study arm	Comparative arm	Study arm	Comparative arm
Miller *et al*[10]	2012	Afatinib plus best supportive care	Placebo plus best supportive care	390	195	58	59
Mok *et al*[11]	2016	Osimertinib	Intravenous pemetrexed plus either carboplatin or cisplatin	279	140	62	63
Nie *et al*[12]	2018	Osimertinib	Docetaxel plus bevacizumab	74	73	49.4	48.6

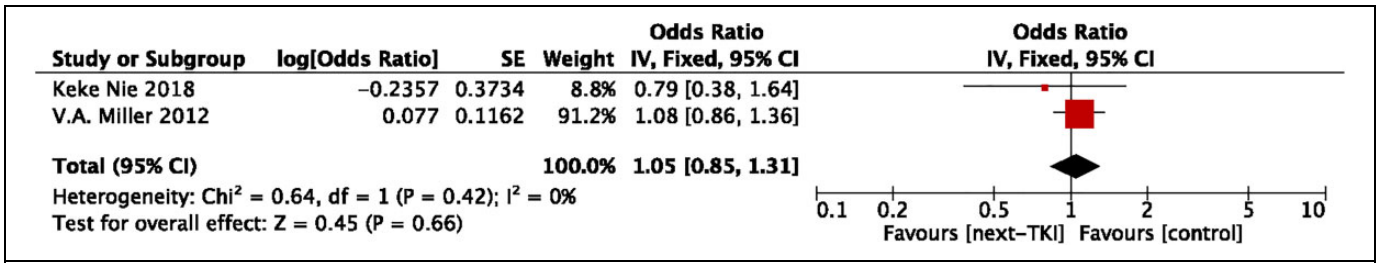

Figure 3. Pooled analysis of OS comparing next-generation EGFR-TKIs versus chemotherapy. EGFR-TKI indicates epidermal growth factor receptor-tyrosine kinase inhibitors; OS, overall survival.

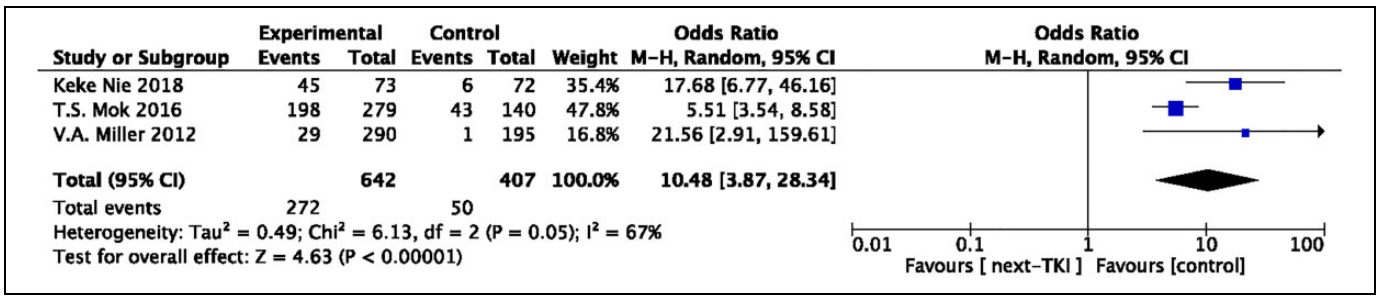

Figure 4. Pooled analysis of ORR comparing next-generation EGFR-TKIs versus chemotherapy. EGFR-TKI indicates epidermal growth factor receptor-tyrosine kinase inhibitors; ORR, objective response rate.

next-generation EGFR-TKIs between patients with EGFR 19 del + T790M mutation and EGFR L858R+T790M mutation are needed.

The improved antitumor activity with second/third-generation TKIs noted in this study might reflect their more potent and irreversible inhibition of EGFR signaling.[19,26] In addition, patients treated with second/third-generation TKIs had statistically significant improvement in the response rate in this study, which are consistent with previous trials.[10-12]

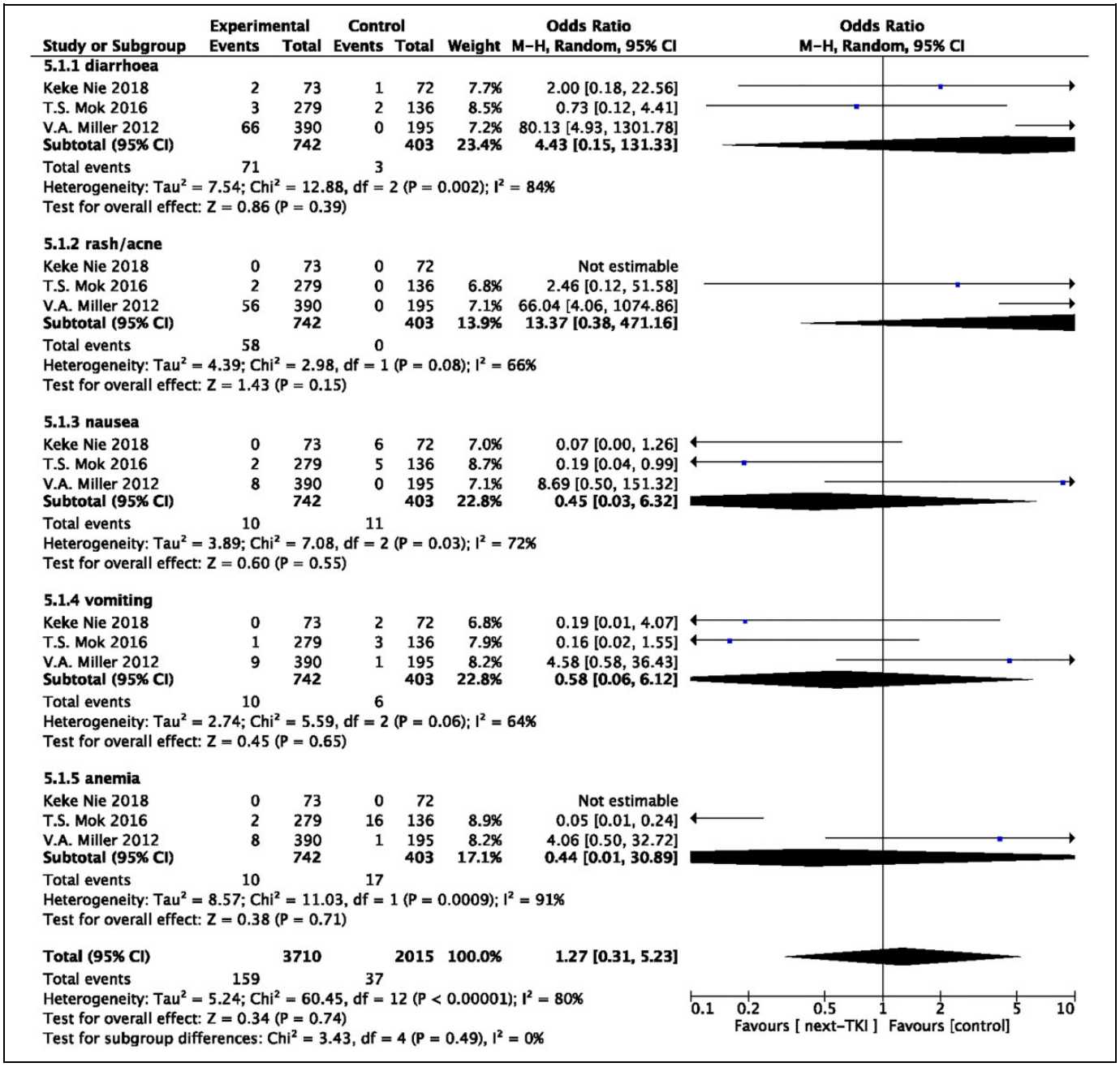

Figure 5. Pooled analysis of AEs comparing next-generation EGFR-TKIs versus chemotherapy. AEs indicates adverse events; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors.

Both treatments showed comparable AE profile, which will be useful in the consideration of second/third-generation TKIs for patients with EGFR mutation–positive NSCLC after first-line EGFR-TKI therapy. This finding suggests that the systematically established safety used in this trial worked well to keep patients on treatment, achieving the maximum benefit from next-generation TKIs. All AEs were manageable and predictable, and with low discontinuation rates, indicating that proactive supportive therapy and dose modification were an adequate strategy to select EGFR inhibition.

In this systematic analysis assessing effect of next-generation TKIs in patients with advanced NSCLC after failure on first-generation EGFR-TKIs, there are some limitations that should not be ignored. First, the current study on the rate of OS provided insufficient data. Thus, there was no strong statistical evidence to be analyzed; Secondly, as this study was a study-level meta-analysis, imbalance existed between the 2 groups due to different qualities and different uses of EGFR-TKIs of the included studies, and the findings of the current study might be affected by clinical heterogeneity among the trials; Thirdly,

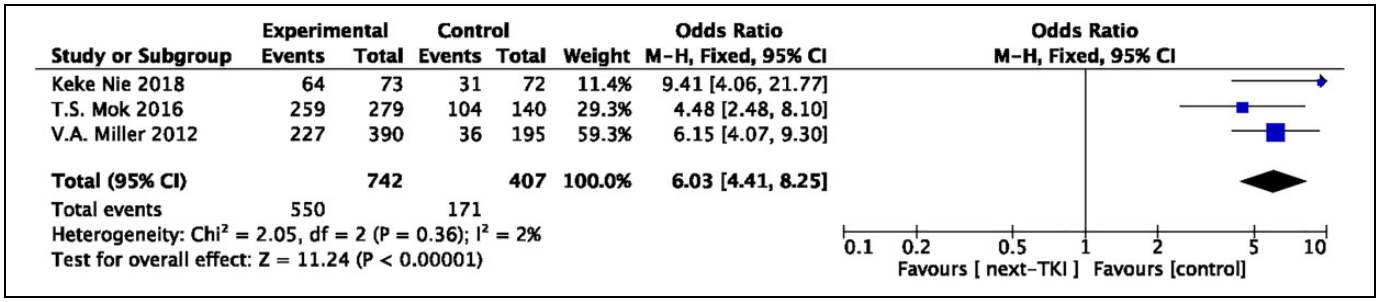

Figure 6. Pooled analysis of DCR comparing next-generation EGFR-TKIs versus chemotherapy. DCR indicates disease controlled rate; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors.

subgroup analysis of EGFR mutations in the 2 cohorts did not provide enough data on subtype, so we could not extract subgroup data from the literature.

Conclusion

Acquired resistance refers to disease progression after response to first-generation EGFR-TK; the survival outcome is dismal if resistance occurs. Our data showed that next-generation EGFR-TKI could prolong PFS and improve the response rate in patients with NSCLC who failed first-generation EGFR-TKI.

Relevant clinical studies have been conducted to develop the paradigm of "personalized" medicine in the treatment of NSCLC, at least in an oncogene-driven subset of patients; examples include mutations in the *EGFR* gene. From an efficacy standpoint, further trials on biomarkers that will benefit patients by molecular stratification, which can be instructive in guiding treatment decisions, with manageable AEs. It is important to consider the risk of AEs when choosing treatment, particularly in patients with underlying immune dysfunction.

Declaration of Conflicting Interests

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