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Efficacy and safety of Kanglaite plus EGFR-TKI in the treatment of advanced non-small cell lung cancer

A meta-analysis of 13 RCTs

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Abstract

Background: Kanglaite (KLT) is a Chinese medicine antitumor drug independently developed in China, which has been widely used in the treatment of advanced non-small cell lung cancer (NSCLC). The purpose of this study was to systematically evaluate the efficacy and safety of KLT plus epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in the treatment of advanced NSCLC.

Methods: Up to September 1, 2022, the databases of PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure, Chinese Biomedical Literature, China Science and Technology Journal, and Wanfang were searched, and the randomized controlled clinical trials (RCTs) of KLT plus EGFR-TKI in the treatment of advanced NSCLC were included. Two researchers independently screened the literature, extracted data, and evaluated the quality of the included literature. Revman5.4 software was used for meta-analysis.

Results: A total of 1057 patients were included in 13 RCTs. The results of meta-analysis showed that KLT plus EGFR-TKI could improve the objective response rate (ORR) (risk ratio (RR) confidence interval (CI) [RR = 1.54, 95% CI: 1.27–1.86, $P < .00001$]), the disease control rate (DCR) (RR = 1.23, 95% CI: 1.14–1.32, $P < .00001$), and quality of life (QOL) (RR = 1.79, 95% CI: 1.36–2.36, $P < .0001$) in patients with advanced NSCLC. The percentages of $CD3^+$T cells (standardized mean difference [SMD = 2.37, 95% CI: 0.80–3.93, $P = .003$]), $CD4^+$T cells (SMD = 1.39, 95% CI: 0.85–1.93, $P < .00001$), NK cells (SMD = 1.59, 95% CI: 0.88–2.30, $P < .0001$), and $CD4^+/CD8^+$ratio (SMD = 0.37, 95% CI: 0.19–0.55, $P < .0001$) were also increased. However, the results of subgroup analysis showed that in patients with EGFR mutation NSCLC, compared with EGFR-TKI alone, KLT plus EGFR-TKI did not significantly increase ORR and DCR (RR = 1.43, 95% CI: 0.88–2.32, $P = .15$; RR = 1.07, 95% CI: 0.96–1.20, $P = .21$). In terms of adverse events of drugs, the incidence of diarrhea, rash, anorexia, nausea and vomiting, liver and renal function damage of KLT plus EGFR–TKI was similar to that of EGFR-TKI alone ($P > .05$).

Conclusion: KLT plus EGFR-TKI has some clinical benefits and good safety compared with EGFR-TKI alone in the treatment of advanced NSCLC. However, it seems that patients with EGFR mutations do not get significant clinical benefits, and more high-quality RCTs are needed to prove the efficacy of the combined regimen.

Abbreviations: CI = confidence interval, CR = complete response, DCR = disease control rate, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, KLT = Kanglaite, NSCLC = non-small cell lung cancer, ORR = objective response rate, PR = partial response, QOL = quality of life, RCTs = randomized controlled clinical trials, RR = risk ratio, SMD = standardized mean difference, TCM = traditional Chinese medicine.

Keywords: EGFR, Kanglaite, meta-analysis, non-small cell lung cancer, TKI

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethical approval was not necessary, because this article is a meta-analysis and it does not involve the participation of ethics committee.

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1. Introduction

According to the annual statistics of GLOBOCAN 2020, lung cancer is still the malignant tumor with the highest mortality in the world.[1] More than 80% of all lung cancer patients are non-small cell lung cancer (NSCLC).[2,3] As the early clinical symptoms of lung cancer are not obvious and the disease progresses rapidly, most patients are diagnosed in an advanced stage and lose the best opportunity for surgical treatment. For a long time in the past, advanced NSCLC patients mainly rely on chemotherapy to prolong overall survival. The standard platinum-containing dual-drug regimen can delay the development of patients' disease to some extent, but the curative effect is not ideal. The median overall survival is only about 10 months,[4,5] the adverse reactions of chemotherapy are large, and the quality of life of patients is significantly reduced. With the continuous application of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in the clinic, the clinical efficacy of patients with advanced NSCLC has been significantly improved.[6] Although EGFR-TKI reduces the incidence of hematological adverse reactions compared with chemotherapy, skin toxicity and gastrointestinal adverse reactions can also adversely affect patients' quality of life and treatment compliance. Inevitably, after a period of EGFR-TKI treatment, the vast majority of patients will develop drug resistance.[7] At the same time, some patients with EGFR mutation did not show a good clinical response at the beginning of treatment.[8] Therefore, to improve efficacy, overcome drug resistance, and reduce adverse reactions, combination therapy based on EGFR-TKI may be a better choice.

The main ingredient of Kanglaite (KLT) is Coix seed, a traditional Chinese medicine (TCM), which is a broad-spectrum anticancer drug, which can inhibit the growth of tumor cells, improve the immune function of patients and reduce the occurrence of complications.[9] As early as 1995, KLT injection has been approved by the Chinese State Food and Drug Administration for the treatment of various malignant tumors. KLT is also the first TCM approved by the US Food and Drug Administration to conduct phase III clinical trials of solid tumors.[10] In recent years, the efficacy of KLT in pancreatic cancer, liver cancer, and lung cancer has been clinically verified.[11–13]

Previous studies have shown that KLT injection combined with chemotherapy can significantly improve the efficacy of advanced NSCLC patients and reduce the adverse reactions caused by chemotherapy.[14] To explore whether KLT plus EGFR-TKI has the same effect of reducing toxicity and enhancing efficacy in the treatment of advanced NSCLC, there are many related studies in recent years, and the conclusions are not completely consistent. Therefore, in this study, meta-analysis was used to systematically evaluate the efficacy and safety of KLT plus EGFR-TKI compared with EGFR-TKI alone in the treatment of patients with advanced NSCLC, to provide the evidence-based basis for clinical rational drug use.

2. Materials and Methods

2.1. Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15] The systematic literature search was performed through PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, China Science and Technology Journal Database, and Wanfang Database, covering all articles published up to September 1, 2022. The following keywords were used to retrieve articles: Non-small cell lung cancer, NSCLC, KLT, EGFR-TKI, Gefitinib, Erlotinib, Icotinib, Afatinib, Dacomitinib, Osimertinib, Almonertinib, and Furmonertinib. References of the retrieved publications were also screened. The search strategy for PubMed is described as follows:

#1 "Carcinoma, Non-Small-Cell Lung" [Mesh]

#2 "Non small Cell Lung Cancer" OR "Non-Small Cell Lung Cancer" OR "Non-Small Cell Lung Carcinoma" OR "Carcinoma, Non-Small Cell Lung" OR "Non Small Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinomas" OR "Lung Carcinomas, Non-Small-Cell" OR "Lung Carcinoma, Non-Small-Cell" OR "Carcinomas, NonSmall-Cell Lung" OR "Carcinoma, Non Small Cell Lung" [Title/ Abstract]

#3 #1 OR #2

#4 "Kanglaite" OR "Coix Seed oil" [Title/ Abstract]

#5 "epidermal growth factor receptor-tyrosine kinase inhibitor" OR "EGFR-TKI" OR "Gefitinib" OR "Erlotinib" OR "Icotinib" OR "Afatinib" OR "Dacomitinib" OR "Osimertinib" OR "Almonertinib" OR "Furmonertinib" [Title/ Abstract]

#6 #3 AND #4 AND #5

Other databases use similar search formulas.

2.2. Literature inclusion and exclusion criteria

2.2..1. Inclusion criteria.

(1) Participants: Stage III/IV patients with pathologically diagnosed NSCLC and unable to undergo radical surgery; Karnofsky performance status (KPS) ≥ 60; expected survival time more than 3 months; at least one measurable lesion; adequate organs function (heart, liver, kidney, bone marrow, and other important organs); no previous EGFR-TKI treatment.

(2) Type of study: randomized controlled clinical trials (RCTs)

(3) Intervention: the experimental group was treated with KLT plus EGFR-TKI, and the control group was treated with EGFR-TKI alone. EGFR-TKI includes Gefitinib, Erlotinib, Icotinib, Afatinib, Dacomitinib, Osimertinib, Almonertinib, and Furmonertinib.

(4) Outcome indicators: objective response rate (ORR), disease control rate (DCR), quality of life (QOL), immune function (the percentages of $CD3^+$T cells, $CD4^+$T cells, $CD8^+$T cells, NK cell, and CD4+/CD8+ratio) and adverse events. The results were divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1). The ORR was calculated as the sum of the CR and PR rates. The DCR was calculated as the sum of the CR, PR, and SD rates. If the KPS score increased by 10 points or more after treatment, the patient's QOL was considered to be improved.

2.2.2. Exclusion criteria. Non RCTs; studies included patients with small cell lung cancer; reviews, case reports, conference summaries and repeated studies; and the data are incomplete and the original data are not available.

2.3. Data extraction and literature quality evaluation

Data were independently screened, extracted, and cross-checked by two reviewers (DL Li and WQ Li). If there is any disagreement in the process, the decision will be made through discussion or by referring to the opinions of the third reviewer (Che). The extracted data mainly include first author name, country, year of publication, TNM stage of the tumor, number of cases, the average age of patients, therapeutic regimens, number of treatment cycles, EGFR gene status, and outcome indicators. If there is a lack of important information in the study, try to contact the first author or corresponding author by email to further obtain unpublished data. The Cochrane

risk of bias tool[16] was used to evaluate the quality of each RCTs included. The risk of bias was evaluated from seven items: selection bias (random sequence generation, allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other biases. Each item was classified as "low risk of bias," "unclear risk of bias" and "high risk of bias."

2.4. Statistical analysis

The Review Manager version 5.4 (Nordic Cochran Centre, Copenhagen, Denmark) software was used to perform the meta-analysis. For dichotomous data, relative risk (RR) and 95% confidence intervals (CI) were used as evaluation indexes. For continuous variables, standard mean difference (SMD) and 95% CI were used for effect pooled analysis. All P values were 2-sided, and $P < .05$ was considered statistically significant. The heterogeneity was tested by Q and I^2 tests. When the heterogeneity exists ($I^2 > 50\%$ or $P < .1$), the random effect model was used for a meta-analysis, otherwise, the fixed effect model was used. Sensitivity analysis was used to test the stability of the results and funnel plots were used to evaluate publication bias.

3. Results

3.1. Literature search and study characteristics

A total of 68 articles were retrieved, and 37 repeated articles were excluded by title, year of publication, and author information. Then after reading abstracts and full-text screening, 18 articles that did not meet the criteria were excluded and finally included 13 studies[17–29] (Fig. 1). There were 1057 patients with advanced NSCLC, of which 531 patients received KLT plus EGFR-TKI and 526 patients received EGFR-TKI alone.

The quality evaluation of the included studies is shown in Table 1. Key baseline characteristics of patients were adequately described in all included studies, as shown in Table 2. Of these, 11 studies[17–19,21–26,28,29] were KLT plus gefitinib versus gefitinib alone, and the other 2 studies[20,27] were KLT plus erlotinib versus erlotinib alone and KLT plus icotinib versus icotinib alone. Five studies[17,19,24–26] included patients with EGFR mutations, and 8 studies[18,20–23,27–29] did not account for EGFR status.

3.2. ORR

Ten studies[18–21,23–25,27–29] provided ORR data, and the results of the heterogeneity test showed that the heterogeneity among the

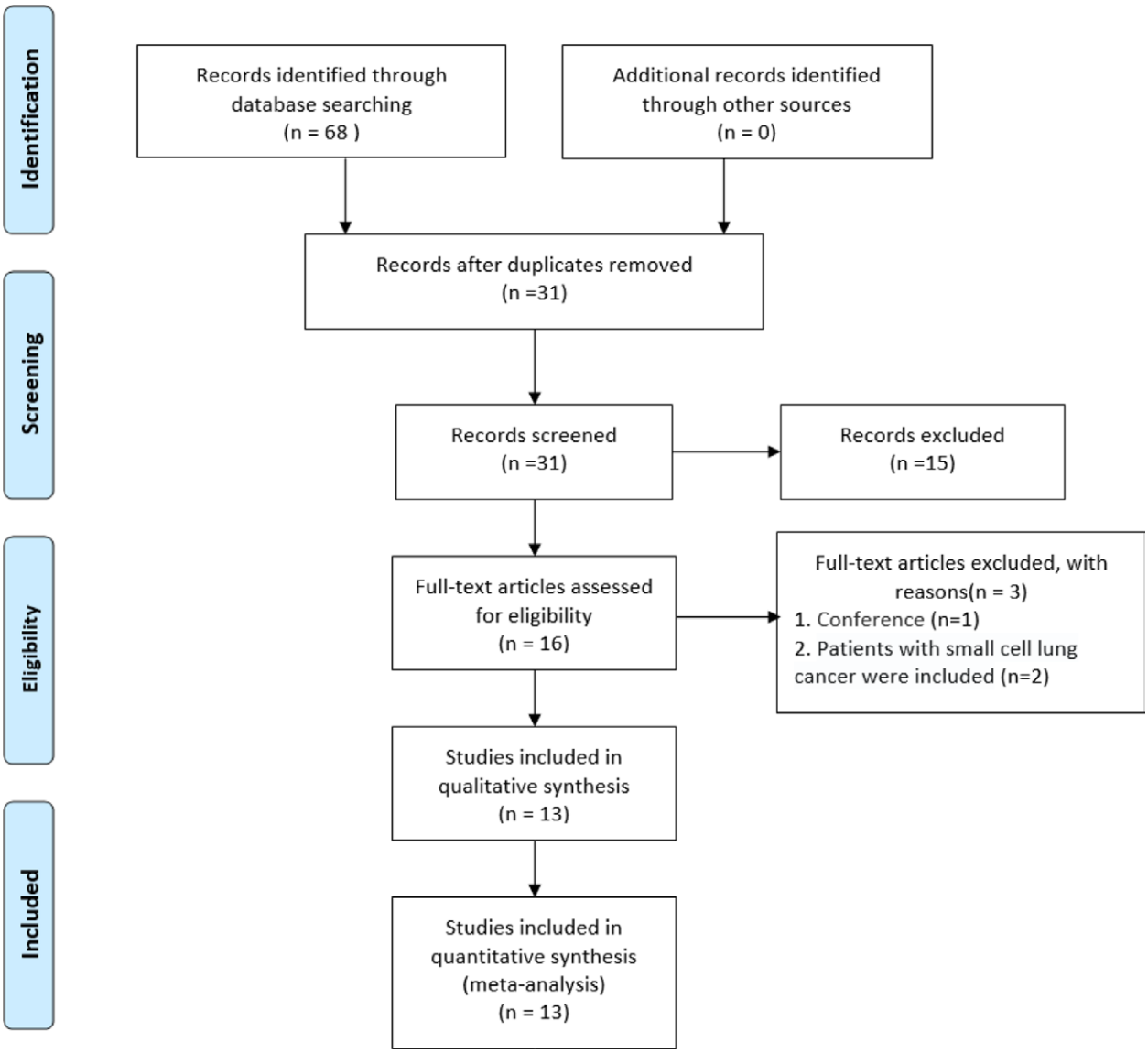

Figure 1. Literature screening flow chart.

Table 1

The methodological quality of the included studies was assessed using the Cochrane "Risk of Bias" tool.

	Selection bias						
Study	**Random sequence generation**	**Allocation concealment**	**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
Cai 2021	?	?	?	?	+	+	?
Zeng 2014	-	?	?	?	+	+	?
Dai 2021	+	?	?	?	+	+	?
Guo 2013	?	?	?	?	+	+	?
Li 2020	?	?	?	?	+	+	?
Ning 2015	+	?	?	?	+	+	?
Qian 2004	?	?	?	?	+	+	?
Shi 2013	?	?	?	?	+	+	?
Wang 2017	?	?	?	?	+	+	?
Yang 2016	+	?	?	?	+	+	?
Yang 2016	+	?	?	?	+	+	?
Zhang 2011	?	?	?	?	+	+	?
Zhang 2014	?	?	?	?	+	+	?

? = unclear risk of bias, + = low risk of bias, - = high risk of bias.

studies was small ($P = .78$, $I^2 = 0\%$). Fixed-effects model analysis showed that the ORR of patients with advanced NSCLC in the KLT plus EGFR-TKI group was significantly higher than that in the EGFR-TKI group (42.6 vs 27.5%, RR = 1.54, 95% CI: 1.27–1.86, $P < .00001$). See Figure 2.

3.3. DCR

Ten studies[18–21,23–25,27–29] provided DCR data, and the results of the heterogeneity test showed that the heterogeneity among the studies was small ($P = .1$, $I^2 = 39\%$). Fixed-effects model analysis showed that the DCR of patients with advanced NSCLC in the KLT plus EGFR-TKI group was significantly higher than that in the EGFR-TKI group (86.4 vs 70.4%, RR = 1.23, 95% CI: 1.14–1.32, $P < .00001$). See Figure 3.

3.4. Results of subgroup analysis of ORR and DCR

To screen the population most likely to benefit from KLT plus EGFR-TKI and the best treatment model, we performed a subgroup analysis of ORR and DCR according to EGFR gene status, mean age of patients, type of EGFR-TKI, KLT administration mode, and the number of treatment cycles. The results of subgroup analysis showed that KLT plus EGFR-TKI could not significantly improve ORR and DCR in patients with EGFR mutations NSCLC compared with EGFR-TKI alone (RR = 1.43, 95% CI: 0.88–2.32, $P = .15$; RR = 1.07, 95% CI: 0.96–1.20, $P = .21$). Intravenous drip of KLT can significantly improve the ORR and DCR of patients with NSCLC (RR = 1.47, 95% CI: 1.21–1.78, $P < .0001$; RR = 1.29, 95% CI: 1.17–1.42, $P < .00001$), while oral administration of KLT cannot significantly improve the DCR of patients (RR = 1.08, 95% CI: 0.98–1.19, $P = .14$). The combination regimen for 3 cycles could significantly improve the ORR and DCR of NSCLC patients (RR = 1.49, 95% CI: 1.20–1.84, $P = .0003$; RR = 1.34, 95% CI: 1.18–1.53, $P < .0001$), while the combination regimen for 2 cycles had no significant improvement on ORR (RR = 1.43, 95% CI: 0.97–2.11, $P = .07$). Both KLT plus gefitinib and erlotinib/icotinib can significantly improve the ORR and DCR of NSCLC patients ($P < .05$). In addition, compared with EGFR-TKI alone, the combined regimen can significantly improve the ORR and DCR of NSCLC patients of all ages ($P < .05$). See Tables 3 and 4.

3.5. QOL

Five studies[17,24,27–29] evaluated the effect of KLT plus EGFR-TKI on patients' QOL, and the results of the heterogeneity test showed that the heterogeneity among the studies was small ($P = .73$, $I^2 = 0\%$). Fixed-effects model analysis showed that the QOL of patients with advanced NSCLC in the KLT plus EGFR-TKI group was significantly higher than that in the EGFR-TKI group (RR = 1.79, 95% CI: 1.36–2.36, $P < .0001$). See Figure 4.

3.6. Cellular immune function

Six included studies[17–19,22,26,27] reported the percentage data of $CD3^+$T cells and $CD4^+$T cells, and heterogeneity test results showed significant heterogeneity among studies ($P < .00001$, $I^2 = 98\%$; $P < .00001$, $I^2 = 87\%$).The random-effects model analysis showed that the percentage of $CD3^+$T and $CD4^+$T cells in NSCLC patients could be significantly increased in KLT plus EGFR-TKI group compared with EGFR-TKI alone group (SMD = 2.37, 95% CI: 0.80–3.93, $P = .003$; SMD = 1.39, 95% CI: 0.85–1.93, $P < .00001$). See Figure 5A and B. The percentage of $CD8^+$T cells was reported in the 3 included studies,[19,22,26] and the heterogeneity test showed significant heterogeneity among the studies ($P < .00001$, $I^2 = 98\%$). Random-effects model analysis showed that KLT plus EGFR-TKI did not increase the percentage of $CD8^+$T cells in NSCLC patients compared with EGFR-TKI alone (SMD = 0.62, 95% CI: -0.44–1.69, $P = .25$). As shown in Figure 5C. NK cell percentage and $CD4^+/CD8^+$ ratio were reported in 5 included studies.[17,19,22,26,27] Based on the heterogeneity test results (NK cells: $P = .33$, $I^2 = 14\%$; $CD4^+/CD8^+$: $P < .00001$, $I^2 = 91\%$), the percentage of NK cells was analyzed by the fixed-effects model, and the ratio of $CD4^+/CD8^+$ was analyzed by random-effects model. The results showed that KLT plus EGFR-TKI could significantly increase the percentage of NK cells and CD4+/$CD8^+$ ratio in NSCLC patients (SMD = 1.59, 95% CI: 0.88–2.30, $P < .0001$; SMD = 0.37, 95% CI: 0.19–0.55, $P < .0001$). See Figure 5D and E.

3.7. Adverse events

In terms of adverse events of drugs, the incidence of diarrhea, rash, anorexia, nausea and vomiting, liver and renal function damage of KLT plus EGFR-TKI was similar to that of EGFR-TKI alone ($P > .05$). See Table 5.

3.8. Sensitivity analysis and publication bias

Sensitivity analysis was performed for each meta-analysis, and each included study was excluded one by one before effect size was pooled. The RR and SMD values and 95% CI obtained did not change significantly, indicating that the results were stable. The funnel plots with ORR and DCR as indicators were basically symmetric, suggesting no significant publication bias. See Figures 6 and 7.

Table 2

Basic characteristics of included literature.

Study	TNM stage	Number of patients		Male/female		Average age (years)		Treatment scheme		Treatment cycle	Whether the subjects had EGFR mutations	Outcome indicators
		Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group			
Zeng 2014	IIIB–IV	23	23	6/17	5/18	52.3	50.9	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Yes	③④⑤
Cai 2021	III–IV	39	39	23/16	24/15	60.03	60.84	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Unclear	①②④⑤
Dai 2021	IIIB–IV	48	48	26/22	27/21	57.6	56.9	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Yes	①②④⑤
Guo 2013	IIIB–IV	32	31	-	-	-	-	Con + Kanglaite 100mL ivdrip bid	Erlotinib 150mg po qd	3	unclear	①②⑤
Li 2020	IIIB–IV	50	50	27/23	29/21	55.29	54.26	Con + Kanglaite 2.7g po qid	Gefitinib 250mg po qd	-	Unclear	①②⑤
Ning 2015	IIIB–IV	93	93	57/36	56/37	53.03	52.95	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Unclear	④
Qian 2004	IIIB–IV	12	13	-	-	-	-	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Unclear	①②⑤
Shi 2013	IIIB–IV	25	20	7/18	5/15	51.4	50.9	Con + Kanglaite 100mL ivdrip qd	Gefitinib 250mg po qd	2	Yes	①②③
Wang 2017	IIIB–IV	40	40	16/24	17/23	-	-	Con + Kanglaite 2.7g po qid	Gefitinib 250mg po qd	-	Yes	①②⑤
Yang 2016	IIIB–IV	32	32	18/14	18/14	56.24	54.84	Con + Kanglaite 200mL ivdrip qd	Gefitinib 250mg po qd	2	Yes	④
Yang 2016	IIIB–IV	43	43	24/19	23/20	65.46	65.47	Con + Kanglaite 200mL ivdrip qd	Icotinib 125mg po tid	3	Unclear	①②③④⑤
Zhang 2011	III–IV	39	39	18/21	18/21	-	-	Con + Kanglaite 100mL ivdrip qd	Gefitinib 250mg po qd	3	Unclear	①②③⑤
Zhang 2014	III–IV	55	55	24/31	26/29	51.9	52.5	Con + Kanglaite 100mL ivdrip bid	Gefitinib 250mg po qd	3	Unclear	①②③⑤

bid = two times per day, Con = control group, ivdrip = intravenous drip, po = oral administration, qd = one time per day, qid = four times per day, ① = ORR, ② = DCR, ③ = quality of life, ④ = cellular immune function, ⑤ = adverse events.

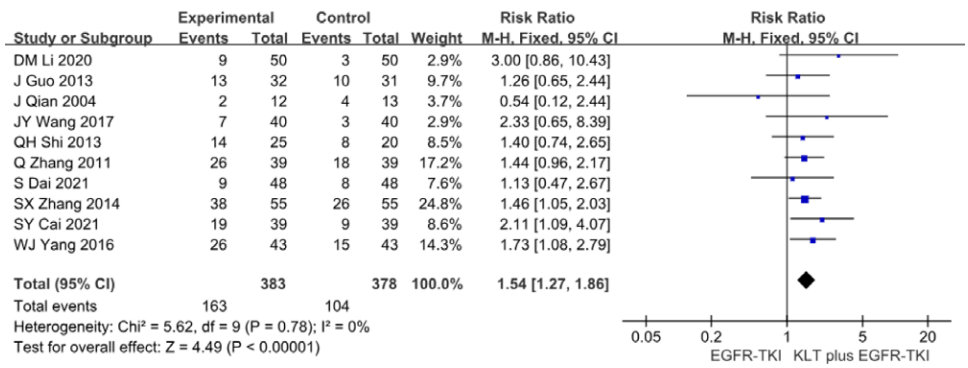

Figure 2. ORR of KLT plus EGFR-TKI versus EGFR-TKI alone. EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, KLT = Kanglaite, ORR = objective response rate.

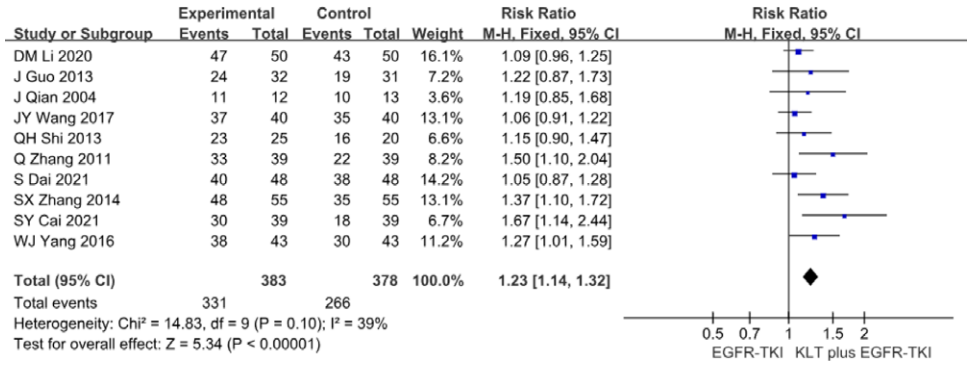

Figure 3. DCR of KLT plus EGFR-TKI versus EGFR-TKI alone. DCR = disease control rate, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, ORR = objective response rate.

Table 3

Subgroup analysis of ORR.

Number of studies		Heterogeneity	RR 95% CI	*P*
Whether the subjects had EGFR mutations				
Yes	3	$P = .65$, $I^2 = 0\%$	1.43 (0.88–2.32)	.15
Unclear	7	$P = .59$, $I^2 = 0\%$	1.56 (1.28–1.91)	<.0001
Average age (yr)				
≥60	2	$P = .63$, $I^2 = 0\%$	1.88 (1.27–2.76)	.001
<60	4	$P = .64$, $I^2 = 0\%$	1.49 (1.13–1.98)	.005
Kanglaite combined with EGFR-TKI				
Kanglaite combined with gefitinib	8	$P = .66$, $I^2 = 0\%$	1.54 (1.24–1.91)	<.0001
Kanglaite combined with erlotinib/icotinib	2	$P = .44$, $I^2 = 0\%$	1.54 (1.05–2.27)	.03
The mode of administration of Kanglaite				
Oral administration	2	$P = .78$, $I^2 = 0\%$	2.67 (1.09–6.50)	.03
Intravenous drip	8	$P = .79$, $I^2 = 0\%$	1.47 (1.21–1.78)	<.0001
Treatment cycle				
2	4	$P = .36$, $I^2 = 8\%$	1.43 (0.97–2.11)	.07
3	4	$P = .88$, $I^2 = 0\%$	1.49 (1.20–1.84)	.0003

EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, ORR = objective response rate, RR = risk ratio.

Table 4

Subgroup analysis of DCR.

	Number of studies	Heterogeneity	RR 95% CI	*P*
Whether the subjects had EGFR mutations				
Yes	3	$P = .83$, $I^2 = 0\%$	1.07 (0.96–1.20)	.21
Unclear	7	$P = .12$, $I^2 = 40\%$	1.31 (1.18–1.44)	<.00001
Average age (yr)				
≥60	2	$P = .20$, $I^2 = 40\%$	1.42 (1.16–1.74)	.0008
<60	4	$P = .27$, $I^2 = 24\%$	1.16 (1.05–1.28)	.003
Kanglaite combined with EGFR-TKI				
Kanglaite combined with gefitinib	8	$P = .05$, $I^2 = 51\%$	1.19 (1.06–1.33)	.002
Kanglaite combined with erlotinib/icotinib	2	$P = .87$, $I^2 = 0\%$	1.25 (1.03–1.51)	.02
The mode of administration of Kanglaite				
Oral administration	2	$P = .74$, $I^2 = 0\%$	1.08 (0.98–1.19)	.14
Intravenous drip	8	$P = .30$, $I^2 = 16\%$	1.29 (1.17–1.42)	<.00001
Treatment cycle				
2	4	$P = .16$, $I^2 = 41\%$	1.22 (1.06–1.41)	.005
3	4	$P = .78$, $I^2 = 0\%$	1.34 (1.18–1.53)	<.0001

DCR = disease control rate, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, RR = risk ratio.

4. Discussion

Advanced NSCLC is aggressive, has a high recurrence and metastasis rate, and the 5-year overall survival rate is only about 5%.[30] There are still challenges in treatment. In recent years, molecular targeted therapy, represented by EGFR-TKI, has brought a new treatment choice for advanced NSCLC patients with EGFR mutations due to the advantages of convenient administration, precise efficacy, and good patient tolerance. EGFR-TKI can promote the apoptosis of tumor cells

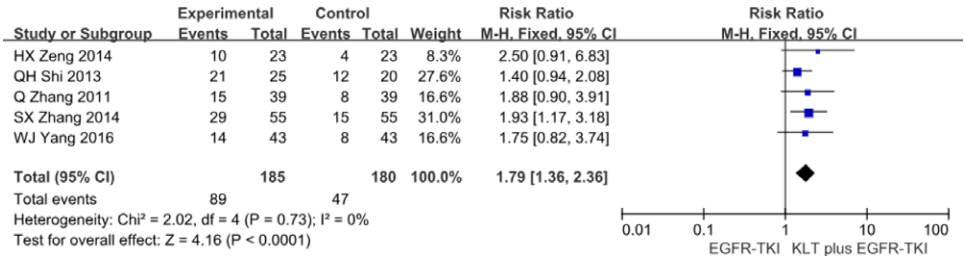

Figure 4. QOL of KLT plus EGFR-TKI versus EGFR-TKI alone. EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, KLT = Kanglaite, QOL = quality of life.

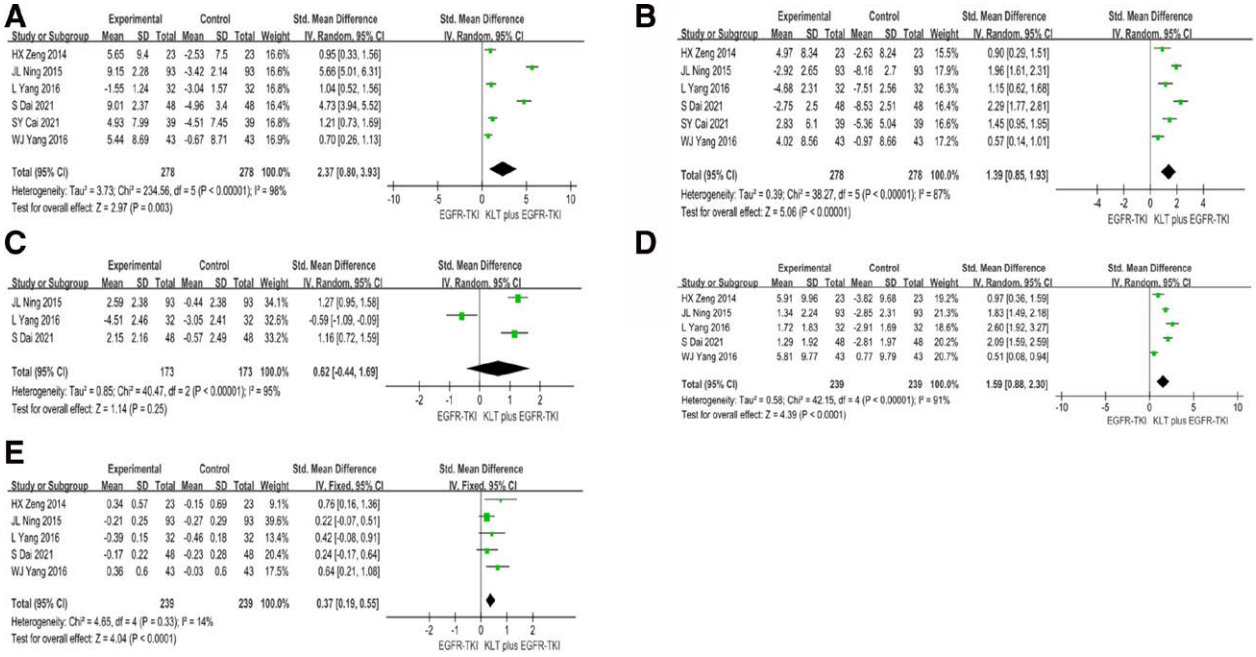

Figure 5. Cellular immune function of KLT plus EGFR-TKI versus EGFR-TKI alone. (A) Percentage of CD3⁺T cells, (B) Percentage of CD4⁺T cells, (C) Percentage of CD8⁺T cells, (D) Percentage of NK cells, (E) CD4⁺/CD8⁺ ratio. EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, KLT = Kanglaite.

Table 5

Comparison of adverse reactions between KLT plus EGFR-TKI and EGFR-TKI alone in the treatment of non-small cell lung cancer.

Adverse reactions	Number of studies	Heterogeneity	RR 95% CI	*P*
Diarrhoea	7	$P = .51$, $I^2 = 0\%$	0.80 (0.57–1.11)	.18
Rash	8	$P = .86$, $I^2 = 0\%$	0.79 (0.58–1.08)	.14
Anorexia	3	$P = .90$, $I^2 = 0\%$	0.89 (0.49–1.65)	.72
Nausea and vomiting	3	$P = .86$, $I^2 = 0\%$	0.77 (0.40–1.46)	.42
Renal function damage	2	$P = .37$, $I^2 = 0\%$	1.00 (0.18–5.64)	1.00
Liver function damage	6	$P = .68$, $I^2 = 0\%$	1.06 (0.68–1.65)	.80

EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, KLT = Kanglaite, RR = risk ratio.

by blocking the signal transduction pathway, thus delaying the progress of the disease.[31] Although the efficacy of EGFR-TKI is significant, the vast majority of patients will inevitably develop drug resistance during EGFR-TKI treatment,[7] which significantly affects the clinical benefits of patients. Some studies have shown that Chinese herbal medicine extract can overcome the drug resistance to EGFR-TKI and enhance the efficacy of anti-EGFR in the treatment of advanced NSCLC.[32,33] For advanced NSCLC, TCM therapy is an effective adjunct to anti-EGFR therapy.[33] The results of a clinical trial showed that TCM combined with EGFR-TKI could significantly prolong the survival time of patients with advanced EGFR mutation compared with EGFR-TKI alone.[34] KLT, as a kind of TCM, a meta-analysis of 27 RCTs shows that KLT combined with chemotherapy can significantly improve efficacy, reduce the adverse reactions of chemotherapy, and improve the immune function of patients with advanced NSCLC.[10] In recent years, there are more and more clinical studies on KLT plus EGFR-TKI in the treatment of advanced NSCLC, and the conclusions are not completely consistent. Therefore, we conducted this meta-analysis to systematically evaluate the efficacy and safety of KLT plus EGFR-TKI compared with EGFR-TKI alone in the treatment of advanced NSCLC, aiming to provide evidence-based evidence for clinical rational drug use.

In our study, a total of 13 RCTs with 1057 patients were included after screening the literature according to inclusion

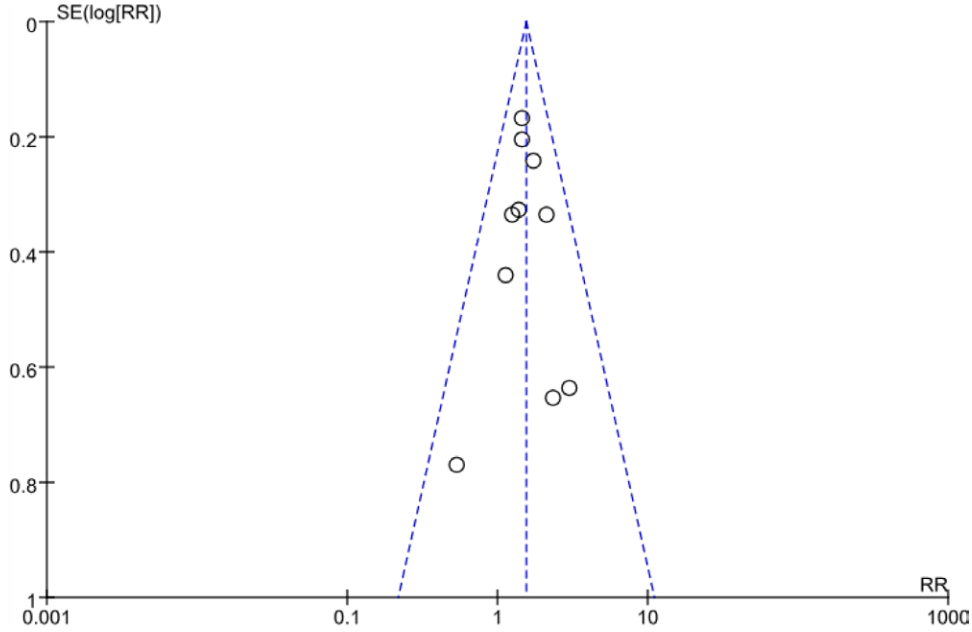

Figure 6. Funnel plot of ORR. ORR = objective response rate.

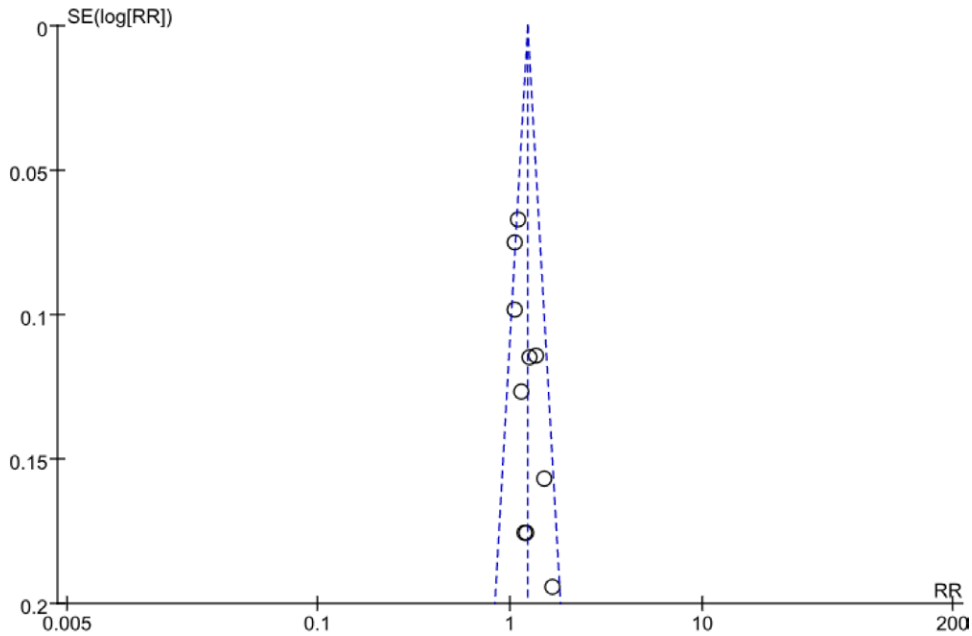

Figure 7. Funnel plot of DCR. DCR = disease control rate.

and exclusion criteria. Our meta-analysis results showed that compared with EGFR-TKI alone, KLT plus EGFR-TKI could improve ORR, DCR, and QOL in patients with advanced NSCLC, increase the percentage of $CD3^+$T cells, $CD4^+$T cells, NK cells, and $CD4^+/CD8^+$ ratio in peripheral blood, and improve the immune function of patients. This is consistent with the results of Kong et al,[35] but the 2 studies[36,37] included in Kong's meta-analysis involved a part of patients with small cell lung cancer and did not conduct subgroup analysis in terms of EGFR gene status, the average age of patients, types of EGFR-TKI and number of treatment cycles. These aspects are most likely to screen out the population that will truly benefit from the combined regimen group and the best treatment mode. Our meta-analysis included more literature published in 2021 to 2022 and excluded studies that included patients with small cell lung cancer. Meanwhile, the results of our subgroup analysis showed that KLT plus EGFR-TKI could not significantly improve the ORR and DCR of patients with EGFR mutations compared with EGFR-TKI alone, which indicated that EGFR-TKI alone was sufficient for patients with EGFR mutations. However, among the 10 RCTs that evaluated ORR and DCR, only 3 RCTs provided specific data on ORR and DCR improvement in patients with EGFR mutations, with relatively limited evidence strength. In addition, the results of subgroup analysis showed that the ORR of patients improved significantly with the increase in the number of treatment cycles (from 2 to 3 cycles). Both KLT plus gefitinib and erlotinib/icotinib can significantly improve the ORR and DCR of NSCLC patients, and the combined regimen group can significantly improve the ORR and DCR

of patients of all ages. Finally, the results of subgroup analysis showed that intravenous drip of KLT was more effective than oral administration of KLT, which could significantly improve the DCR of patients. In terms of safety, the incidence of diarrhea, rash, anorexia, nausea and vomiting, and liver and renal function damage in the KLT plus EGFR-TKI group was similar to that in EGFR-TKI alone group. This shows that KLT does not increase the adverse reactions of anti-EGFR therapy, and KLT plus EGFR-TKI is safe in the treatment of advanced NSCLC.

In our meta-analysis, the ORR and DCR of the control group (EGFR-TKI alone) in the overall population were 27.5% and 70.4%, respectively. The ORR is slightly lower than the 30% to 40% reported in previous clinical trials,[38,39] which may be related to the small sample size of our study. The DCR is roughly comparable to the 70% to 80% reported in previous clinical trials.[38,39] In addition, our study also has its limitations: the included RCTs are single-center, small-sample studies conducted in China, and lack large-sample, global multi-center studies. Most of the RCTs included did not clearly explain random sequence generation, allocation concealment, and blinding. The follow-up time of all RCTs was short, and no long-term survival data such as overall survival, and progression-free survival were provided. There was no report on KLT combined with the second generation EGFR-TKI and the third generation EGFR-TKI, and all the included studies were KLT plus the first generation EGFR-TKI.

In conclusion, KLT plus EGFR-TKI is superior to EGFR-TKI alone in improving ORR, DCR, QOL, and immune function of patients with advanced NSCLC, and has good safety. However, it has no obvious advantage in improving ORR and DCR of EGFR mutation patients. Because there are few studies on patients with EGFR mutations, and the quality of some studies is low, the evidence strength of this result is limited, which needs to be further verified by more strictly designed large samples and multi-center RCTs.

Author contributions

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